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The Genetics of Cognition in Schizophrenia

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List of Publications included in this thesis:

1. **Wootton O**, Dalvie S, Susser E, Gur RC, Stein DJ. Within-individual variability in cognitive performance in schizophrenia: A narrative review of the key literature and proposed research agenda. Schizophrenia Research. 2023 Feb 1;252:329-34.

2. **Wootton O**, Dalvie S, MacGinty R, Ngqengelele L, Susser ES, Gur RC, Stein DJ. Predictors of within-individual variability in cognitive performance in schizophrenia in a South African case-control study. Acta Neuropsychiatrica. 2023 Jun 21:1-23.

3. **Wootton O**, Shadrin AA, Mohn C, Susser E, Ramesar R, Gur RC, Andreassen OA, Stein DJ, Dalvie S. Genome-wide association study in 404,302 individuals identifies 7 significant loci for reaction time variability. Molecular Psychiatry. 2023.

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Date: 4 December 2023

Abstract

The Genetics of Cognition in Schizophrenia

Background: Cognitive impairment is a well-documented feature of schizophrenia and a major determinant of functional outcomes. Cognitive function may be assessed by measuring mean performance measures on cognitive tasks or by measuring variability in performance across tasks or trials of a task that make up a cognitive test battery. Previous research has demonstrated that both cognitive ability and schizophrenia are highly heritable, and that there is a genetic contribution to cognitive impairment in schizophrenia. However, insights into the genetic determinants of cognitive function in schizophrenia remain limited. The overarching aim of the study is to extend current understanding of cognitive impairment in schizophrenia by using previously under-researched or novel metrics of cognitive performance. First, the significance of the phenotype, within-individual variability (WIV) in cognitive performance, was examined in a South African study of people living with schizophrenia. Second, data from the UK Biobank was used to investigate the common genetic determinants of WIV. Third, genetically informed factors corresponding to broad cognitive abilities were used to explore the overlap between the latent cognitive factors, schizophrenia, and schizophrenia symptom dimensions.

Methods: A narrative review of the key literature on the clinical, neural, and genetic correlates of WIV was conducted. Multivariable linear regression analyses were then used to assess the relationship between WIV in cognitive performance and selected demographic and clinical variables in 544 people with schizophrenia and 861 matched controls from a South African case-control study. To explore the common genetic basis of WIV, a genome-wide association study (GWAS) of reaction time variability, a measurement of across-task WIV, was conducted in 404,302 individuals from the UK Biobank, a large population-based cohort. Linkage disequilibrium score regression was used to assess the genetic correlations between reaction time variability and selected neuropsychiatric traits, including schizophrenia. Lastly, Genomic Structural Equation Modelling was applied to cognitive data from the UK Biobank to derive latent factors corresponding to broad dimensions of cognitive function. The overlap

between the latent cognitive factors, schizophrenia, and schizophrenia symptom dimensions was explored using a variety of statistical approaches, including bivariate MiXeR, the conjunctional false discovery rate method, and polygenic risk score analysis.

Results: On a phenotypic level, increased WIV in performance speed across cognitive tests was significantly associated with a diagnosis of schizophrenia, older age, a lower level of education, and a lower score on the global assessment of functioning scale. The GWAS of reaction time variability yielded 161 genome-wide significant single nucleotide polymorphisms distributed across 7 loci, implicating genes involved in synaptic function and neural development. Reaction time variability showed a significant genetic correlation with several traits, including a positive correlation with schizophrenia. Lastly, three latent factors (visuo-spatial, verbal analytic and decision/reaction time) underlying the genetic correlations between the UK Biobank cognitive tests were identified. There was evidence of substantial polygenic overlap between each cognitive factor and schizophrenia but despite the extensive overlap, most significant loci shared between each latent cognitive factor and schizophrenia showed unique patterns of association with the respective factor. Biological annotation of the shared loci implicated gene-sets related to neurodevelopment and neuronal function.

Conclusions: The significant relationship between measurements of WIV in performance speed and schizophrenia as well as global functioning in the disorder supports the use of WIV as a measure of cognitive dysfunction in schizophrenia. This thesis demonstrates that reaction time variability is heritable, has a positive genetic correlation with schizophrenia, and that genes associated with reaction time variability have similar biological functions to those affected in schizophrenia. Lastly, substantial overlap in the common genetic influences of latent cognitive factors and schizophrenia was demonstrated. This research suggests that genes related to neurodevelopment and neuronal function underpin cognitive deficits in schizophrenia.

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Preface

Cognitive impairment is a well-documented feature of schizophrenia and a major determinant of functional outcomes. Previous research has demonstrated that both cognitive ability and schizophrenia are highly heritable, and there is evidence to suggest a genetic contribution to cognitive impairment in schizophrenia. However, there are several gaps in our knowledge of cognition in schizophrenia.

Research Concept and Funding

This thesis aims to use previously under-researched and novel metrics of cognitive function to extend current understanding of cognition in schizophrenia. The candidate independently conceived and conducted the research described in this thesis, with guidance and supervision from their primary supervisor, Dr Shareefa Dalvie, and their co-supervisors, Dr Alexey Shadrin and Professor Dan Stein. The work presented in this thesis was supported by National Institute of Mental Health (NIMH: Grant number U01MH125053), and The Research Council of Norway (275054).

Structure of the Thesis

This thesis is presented as three distinct sections: 1) the demographic, clinical, and functional correlates of within-individual variability in cognitive function in people with schizophrenia in a South African setting, 2) the common genetic determinants of within-individual variability in cognitive function, and 3) the genetic overlap between broad domains of cognitive function and schizophrenia.

The thesis begins with a general introductory chapter and an outline of the aims and objectives. The general introduction is followed by a narrative review focused on within-individual variability in schizophrenia, which is one of the metrics of cognitive function that is investigated in this work. The body of the thesis is comprised of three original research papers, each intended to contribute to the scientific literature on the subject matter. The thesis concludes with a chapter dedicated to discussing and synthesizing the results presented in the thesis.

Ethical Standards

The work described in this thesis was approved by The University of Cape Town Human Research Ethics Committee (reference number - 734/2021). This thesis is a secondary data analysis but all original study protocols comply with the ethical standards of the relevant national and institutional ethics committee and with the Helsinki Declaration of 1975, as revised in 2008.

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Abbreviations

ADHD	Attention-deficit hyperactivity disorder
AIC	Akaike information criterion
ARMS	At-risk mental state
BPRS	Brief Psychiatric Rating Scale
CADD	Combined annotation dependent depletion
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CHC	Cattell-Horn-Carroll
Chr	Chromosome
condFDR	Conditional False Discovery Rate
conjFDR	Conjunctional False Discovery Rate
CNV	Copy number variant
DALY	Disability adjusted life year
df	Degrees of freedom
EFA	Exploratory factor analysis
FDR	False discovery rate
Fluid Int	Fluid intelligence
FUMA	Functional mapping and annotation of genome-wide association studies
GAF	Global Assessment of Functioning Scale
GCA	General cognitive ability
GWAS	Genome-wide association study
h^2_{SNP}	SNP-based heritability
HC	Healthy control
HIV	Human immunodeficiency virus
ICV	Intraindividual coefficient of variation
IQ	Intelligence quotient
ISD	Intra-individual standard deviation
kb	Kilobases
LAVA	Local Analysis of [co]Variant Association

LD	Linkage disequilibrium
LDSC	Linkage disequilibrium score regression
LMIC	Low-and-middle income countries
MAC	Minor allele count
MAF	Minor allele frequency
Matrix	Matrix pattern completion
Num Mem	Numeric memory
Pairs Match	Pairs matching
PAL	Paired associate learning
PANSS	Positive and Negative Syndrome Scale
PennCNB	The University of Pennsylvania Computerized Neurocognitive Battery
PGC	Psychiatric Genomics Consortium
PGS	Polygenic score
Pro Mem	Prospective memory
PRS	Polygenic risk score
PSZ	People with schizophrenia
PTSD	Post-traumatic stress disorder
RDB	RegulomeDB
rg	Genetic correlation
RT	Reaction time
RTV	Reaction time variability
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
SAX	The Genomics of Schizophrenia in the South African Xhosa People
SCID-I	Structured Diagnostic Interview for DSM-IV Axis I Disorders
SCZ	Schizophrenia
SDS	Symbol digit substitution
SE	Standard error
SEM	Structural equation modelling
SNP	Single nucleotide polymorphism

SRMR	Standardized root mean square residual
SST	Stop-signal task
TMT-A	Trail making test-part A
TMT-B	Trail making test-part B
TOP	Thematically Organised Psychosis
Tower	Tower rearranging test
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent Questionnaire
UKB	United Kingdom Biobank
WIV	Within-individual variability

Chapter 1: Introduction

This chapter provides an overview of the key literature pertaining to cognitive impairment in schizophrenia, the genetic underpinnings of schizophrenia, and the genetic basis of cognitive dysfunction in schizophrenia. Next, the research gaps that provided the rationale for the study are outlined. Lastly, a description of the aims and objectives of the thesis is provided.

1.1. Schizophrenia

1.1.1. Epidemiology of Schizophrenia

According to a 2015 systematic review, the lifetime prevalence estimate for schizophrenia (SCZ) is 0.48% (IQR: 0.34 % - 0.85%;(Simeone et al., 2015). Data from low- and middle- income countries (LMICs), including South Africa, is lacking therefore accurate assessment of prevalence in these regions is difficult (Charlson et al., 2018). Sex differences in the prevalence of SCZ are disputed with some studies demonstrating a higher prevalence in males and others finding no difference between the sexes (Charlson et al., 2018; Jongsma et al., 2019; Simeone et al., 2015; Sommer et al., 2020).

Despite the relatively low prevalence of SCZ, it is a leading cause of disability adjusted life years (DALYs) globally (Charlson et al., 2018). In sub-Saharan Africa in 2017, SCZ caused 105.2 (78.9 – 130.8) DALYs per 100,000 population (Gouda et al., 2019). Disability in the disorder may arise from a diverse range of factors including perceptual and cognitive disturbances, difficulties in interpersonal relationships, stigma, and challenges in accessing and maintaining employment (Nowak et al., 2016; Świtaj et al., 2012). Additionally, SCZ is associated with a significant decline in both objective and subjective measures of quality of life (Świtaj et al.,

2012). High excess premature mortality is found across all age groups of individuals with SCZ and may be attributed to high rates of comorbid illness, such as cardiovascular disease, and increased suicide rates (Charlson et al., 2018; Owen et al., 2016).

The economic burden of SCZ is high with healthcare costs as well as disease-related indirect costs, such as loss of income due to unemployment, contributing towards the burden (Chong et al., 2016; Kadakia et al., 2022a). A systematic review of the economic costs of SCZ found that the total cost ranged from 0.02-1.65% of a country's gross domestic product however, data from LMICs is limited (Chong et al., 2016). A study in the United States of America found that indirect costs, such as loss of income due to unemployment and caregiving, make a greater contribution towards the economic burden of SCZ than direct costs (Kadakia et al., 2022a). This finding emphasizes the need for interventions that alleviate symptoms, including cognitive impairment, to minimize disability and indirect costs (Kadakia et al., 2022a).

1.1.2. Symptoms and Natural History of Schizophrenia

SCZ is a psychotic disorder characterized by a range of cognitive, behavioural and perceptual disturbances that cause significant functional impairment (American Psychiatric Association, 2013b). Symptoms may include a combination of positive symptoms (hallucinations and delusions), disorganized thought and behaviours, negative symptoms (avolition, alogia, social withdrawal, restricted affect) and cognitive impairment (American Psychiatric Association, 2013b). The course of disease and symptoms differ between individuals and the severity of symptoms tends to vary during the course of illness (American Psychiatric Association, 2013b; Owen et al., 2016). The onset of SCZ typically occurs from late adolescence until the mid-thirties with an earlier peak age of onset in males (McGrath et al., 2008). Active-phase SCZ is

often preceded by a prodromal period during which a brief limited psychotic episode or attenuated psychotic symptoms may occur (Fusar-Poli et al., 2013).

1.1.3. Genetic Underpinnings of Schizophrenia

SCZ is a complex disorder in that it arises from the interplay of environmental and genetic risk factors (Owen et al., 2016). SCZ is highly heritable with twin and SNP-based estimates of 0.8 and 0.26 respectively (Baselmans et al., 2021; Hilker et al., 2018). Both rare and common variants have shown to contribute towards the genetic risk of SCZ (Marshall et al., 2017; Singh et al., 2022; Trubetskoy et al., 2022). Overlapping genetic risk has been demonstrated between SCZ and other psychiatric conditions such as bipolar mood disorder, autism spectrum disorder, and depression (Nakamura & Takata, 2023; Trubetskoy et al., 2022).

Genome-wide association studies (GWAS) have improved our understanding of complex disorders through the identification of common alleles of small effect that are associated with an increased genetic risk for such disorders. By aggregating the small effects of these alleles, a polygenic risk score (PRS) for the trait may be calculated in order to provide an estimate of an individual's inherited susceptibility to a complex trait (Dudbridge, 2013). The latest SCZ-GWAS by the Psychiatric Genomics Consortium (PGC) included 76,755 people with SCZ and 243,649 controls and identified 287 risk-loci for SCZ, implicating genes that are involved neuronal function (Trubetskoy et al., 2022). However, the 287 risk-loci for SCZ only account for approximately one third of the genetic risk of SCZ (Trubetskoy et al., 2022). Rare variants with large effects, such as copy number variants (CNVs), are hypothesized to account for most of the remaining genetic risk of SCZ (Owen & Williams, 2021; Thygesen et al., 2020; Walsh et al., 2008). CNVs are genomic microdeletions and microduplications that are usually benign

and contribute to genetic variation in populations (Gulsuner & McClellan, 2015; Sebat et al., 2004). A large CNV meta-analysis (21,094 cases; 20,227 controls) by the PGC identified 8 CNVs that were significantly associated with SCZ, with odds ratios (ORs) ranging from 3.8 to infinity (Marshall et al., 2017). Genes impacted by SCZ associated CNVs are disproportionately involved in pathways that are essential for neurodevelopment and cellular signalling (Marshall et al., 2017).

In addition to common SNPs and CNVs, other rare variants, including SNPs and short insertions/deletions (indels) in protein-coding regions, have been implicated in the genetic basis of SCZ (Singh et al., 2022). In a study that analysed whole-exome sequencing data from 24,248 people with SCZ and 97,322 controls, ultra-rare coding variants (variants with a minor allele count ≤ 5 in coding exons) in 10 genes (*SETD1A, CUL1, XPO7, TRIO, CACNA1G, SP4, GRIA3, GRIN2A, HERC1,* and *RB1CC1*) were significantly associated with SCZ risk with ORs ranging from 3-50 (Singh et al., 2022). The identified genes were enriched for expression in the central nervous system and play a role in diverse molecular functions, including synaptic function (Singh et al., 2022).

Findings from studies of both common and rare coding genetic variants associated with SCZ converge, with variants across the spectrum of allele frequencies disrupting many of the same genes, e.g. *GRIN2A* and *SP4* (Nakamura & Takata, 2023). Additionally, genes identified by rare and common variant approaches implicate the same molecular and biological processes, such as chemical synaptic transmission and ion channel or transporter activities, in the pathogenesis of SCZ (Nakamura & Takata, 2023). The convergence of evidence from these studies is promising, however, much of the genetic liability for SCZ remains unexplained. It is

hypothesized that increasing study sample sizes and further analyses, particularly of rare coding variants and CNVs, will facilitate the identification of additional risk variants and a more complete understanding of the genetic determinants of the disorder (Nakamura & Takata, 2023; Singh et al., 2022).

1.1.4. Environmental Risk Factors for Schizophrenia

Several environmental risk factors for SCZ have been identified, many of which affect early neurodevelopment. Risk factors for SCZ that impact early neurodevelopment include maternal infections, maternal stress, nutritional deficiencies, and pregnancy or birth complications that result in foetal hypoxia (Brown, 2011, 2012; Khandaker et al., 2013; Khashan et al., 2008; McGrath et al., 2010). Other potential risk factors include older paternal age, childhood trauma, immigration, season of birth and cannabis use during adolescence (Cantor-Graae & Selten, 2005; Davies et al., 2003; Miller et al., 2011; Moore et al., 2007; Varese et al., 2012).

1.1.5. Cognitive Impairment in Schizophrenia

Global impairment in cognitive function is a well-documented feature of SCZ and an important determinant of functional outcome (Fett et al., 2011; Fioravanti et al., 2012; Heinrichs & Zakzanis, 1998). Cognitive deficits are typically present before the onset of psychotic symptoms and tend to persist over the course of the illness (Mollon & Reichenberg, 2018; Velthorst et al., 2021; Woodberry et al., 2008). Although individuals with SCZ have impaired performance compared to healthy controls across all domains (McCutcheon et al., 2023), deficits are more pronounced in executive function, attention, episodic memory and motor speed (Gur et al., 2015). Cognitive deficits have been demonstrated in unaffected

relatives of individuals with SCZ and this observation, taken together with evidence from molecular genetic studies suggests that there is a genetic basis for cognitive impairment in SCZ (Harvey et al., 2020; Snitz et al., 2006). On a phenotypic level, cognitive deficits appear to be distinct from positive and negative symptoms in SCZ and it is hypothesized that this phenotypic distinction reflects differences in the biological underpinnings of the SCZ symptom dimensions (Legge et al., 2021; Rodriguez-Jimenez et al., 2013).

Cognitive deficits contribute to the economic burden associated with SCZ by increasing both direct healthcare costs and indirect costs associated with the disorder (McCutcheon et al., 2023). Cognitive impairment in SCZ has been associated with reduced treatment adherence, increased duration of in-patient treatment and increased likelihood of hospitalization (Kadakia et al., 2022b; Kitchen et al., 2012). Additionally, cognitive impairment contributes towards unemployment and lost productivity in the disorder and has been associated with lower wages and reduced success of employment interventions, such as supported employment opportunities (Bell & Bryson, 2001; McGurk et al., 2003; Tsang et al., 2010). Given that cognitive deficits are a key determinant of functional outcomes in SCZ and that evidence suggests that there is a biological basis for these deficits, understanding the underlying biology, including the genetic underpinnings, has become a research priority.

1.2. Cognition

Cognition refers to the mental processes involved in the acquisition and processing of information (Colman, 2015). Cognitive performance may be interpreted in terms of domains and functioning (Harvey, 2019). Cognitive domains were initially organised based on the areas of the brain that were hypothesized to be involved in specific cognitive processes (Harvey,

2019). The advent of functional magnetic resonance imaging has improved our understanding of the cognitive domains by allowing for the identification and isolation of brain systems that are activated during specific cognitive tasks (Harvey, 2019).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines 6 principal domains of cognitive function (**Figure 1.1**): perceptual-motor function, language, executive function, learning and memory, complex attention and social cognition (American Psychiatric Association, 2013a). Each domain consists of sub-domains which may be assessed by tasks in a neurocognitive test battery (**Figure 1.1**).

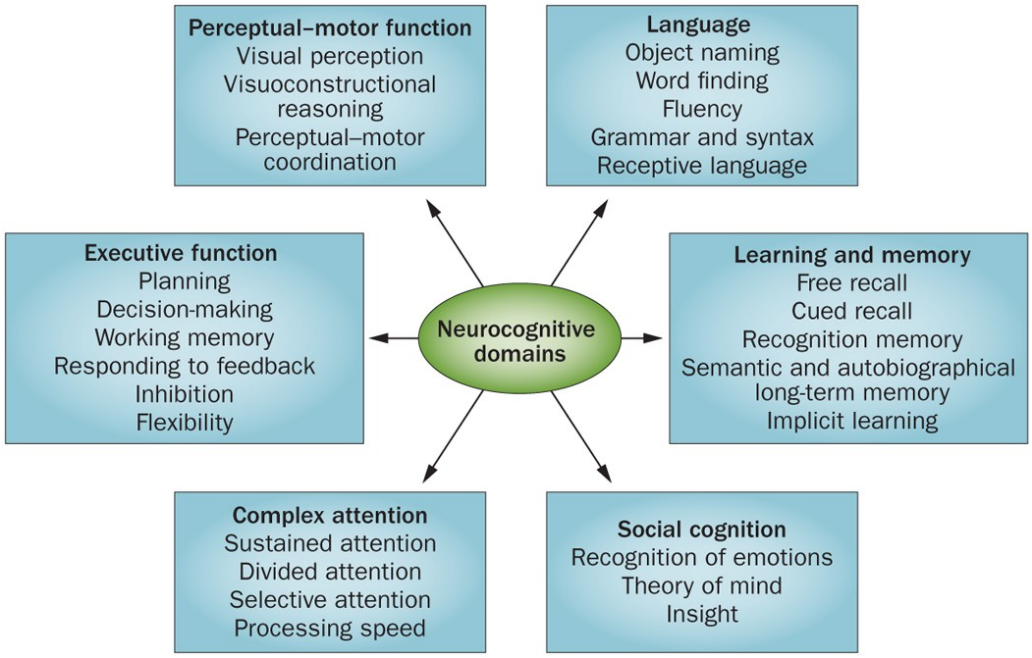

Figure 1. 1: The six domains of cognitive function

The six domains of cognitive function with subdomains. Adapted from Sachdev et al. (2014).

An alternative theory of human cognitive abilities is the Cattell-Horn-Carroll (CHC) theory, which proposes a three-stratum model of human intelligence (Flanagan & Dixon) (Schneider & McGrew, 2018). In the CHC theory, the apex of the model corresponds to a general intelligence "*g*" factor, the mid-level consists of broad cognitive abilities, and the base of the model consists of many narrow cognitive abilities (**Figure 1.2**) (Schneider & McGrew, 2018). The CHC theory provides a framework for the development of modern cognitive test batteries and for the design and interpretation of studies on human intelligence (Flanagan & Dixon). The CHC theory is dynamic and is constantly revised based on current research (Flanagan & Dixon). In the current model of the CHC theory, the base stratum is comprised of over 80 narrow cognitive abilities that correspond to specific skills assessed by a set of highly correlated tasks or tests (e.g. attentional control, perceptual speed, inductive reasoning) (Schneider & McGrew, 2018). The second stratum consists of 8-10 broad cognitive abilities that represent clusters of highly correlated narrow abilities (e.g. fluid reasoning, quantitative knowledge, and processing speed) (Schneider & McGrew, 2018). The *g* factor, which is found at the apex of the model, is discussed in further detail in the next section.

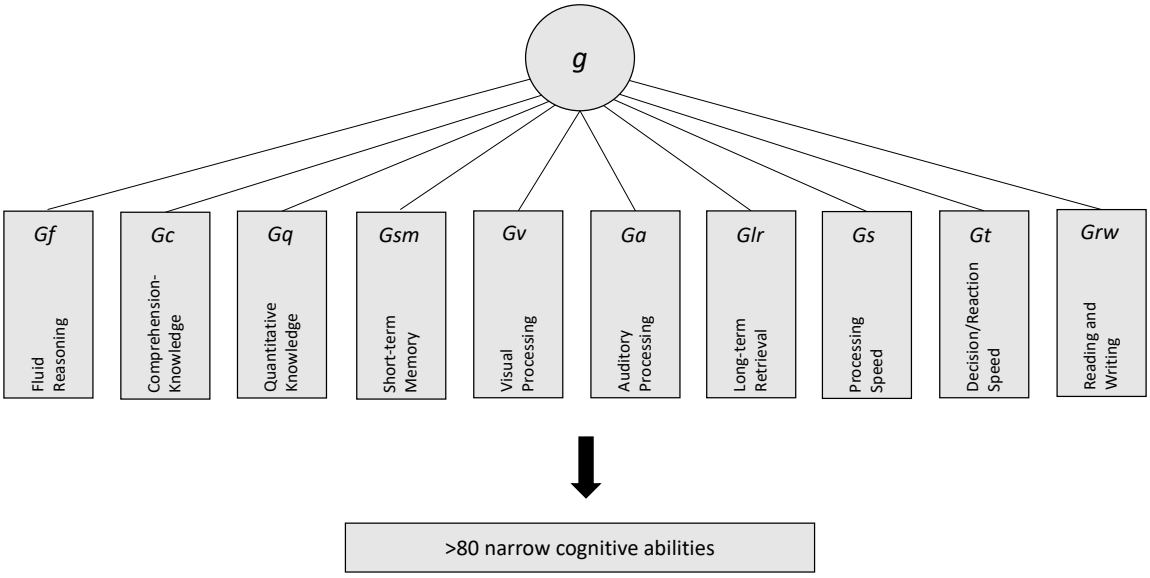

Figure 1. 2: The Cattell-Horn-Carroll Theory of Human Cognitive Abilities
Adapted from Flanagan and Dixon (2014).

1.2.1. Measures of Cognitive Function

Neuropsychological test batteries provide a systematic approach to the assessment of cognitive performance and many have been developed for use in both clinical and research settings (Stebbins, 2007). If a test battery is diverse and reliable, a measure of general cognitive ability (or "*g*") may be calculated based on performance across tasks (Johnson et al., 2004; Johnson et al., 2008). The *g* factor accounts for approximately 40% of the variance in performance across cognitive domains and is stable across the life course (Carroll, 1993; Deary et al., 2013; Deary et al., 2012; Lyons et al., 2017). The "*g*" factor is predictive of educational achievement and attainment, occupational outcomes and measures of physical health (Calvin et al., 2017; Deary et al., 2007; Schmidt & Hunter, 2004).

Typically, differences in mean measures of performance on cognitive tests are used to assess differences in cognitive function between individuals and groups. However, cognitive ability

may also be assessed by examining within-individual variability (WIV) in cognitive function (MacDonald et al., 2009b). WIV in cognitive functioning reflects the extent of the variation in an individual's performance relative to their mean performance and may be assessed in 3 different contexts: across tasks during the same testing session, across trials of the same task during the same testing session and across trials of the same task during different testing sessions (Cole et al., 2011; MacDonald et al., 2009b). WIV captures systematic as opposed to random errors in cognitive performance that reflect the stability of cognitive processing in an individual (MacDonald et al., 2009b). The neural origins of variability in cognitive function remain poorly understood. Variability in cognitive performance has been linked to structural, functional and neurochemical abnormalities in the brain (MacDonald et al., 2009b). Recent evidence suggests that measures of WIV may provide unique insight into cognitive function over and above mean performance measures, such as those used to calculate *g*, and that WIV may better capture differences between groups (Hultsch et al., 2008).

1.2.2. Genetics of Cognition

General cognitive ability, *g*, is heritable (Davies et al., 2018) with SNP-based heritability (h^2_{SNP}) estimates ranging between 0.2 - 0.3 (Plomin & von Stumm, 2018) and an estimated heritability of 0.5 in twin studies (Procopio et al., 2022). Twin studies have demonstrated that the heritability of general cognitive ability increases throughout development with the heritability of *g* increasing from 0.4 during infancy to 0.6 during adulthood (Davies et al., 2011). The heritability of specific cognitive abilities, such as fluid reasoning and processing speed, varies (range: 0.39 – 0.64) and these heritability estimates appear to be constant over the lifespan (Procopio et al., 2022). Additionally, significant genetic correlation exists across cognitive domains (Davies et al., 2011; Plomin & Deary, 2015).

Both common and rare genetic variants contribute towards the heritability of cognitive function (Chen et al., 2023; Davies et al., 2018; Mollon et al., 2023). To date, the largest GWAS meta-analysis of general cognitive ability, which included 300,486 individuals, identified 148 genome-wide significant loci (Davies et al., 2018). The identified loci are enriched for genes associated with neural and cell development (Davies et al., 2018). Findings from a recent analysis of whole-exome sequencing data from 485,930 adults included eight genes *(ADGRB2, KDM5B, GIGYF1, ANKRD12, SLC8A1, RC3H2, CACNA1A and BCAS3)* that influence cognitive function through rare variants with large effects (Chen et al., 2023). The biological pathways through which rare variants may affect cognitive function overlap with those identified in common variant analyses and include synaptic function, neurogenesis, neuronal differentiation, and neuronal development (Chen et al., 2023).

1.3. Genetic Overlap Between Cognition and Schizophrenia

Both twin studies and GWAS have demonstrated that a negative correlation exists between genetic risk for SCZ and the genetic determinants of cognitive ability (Davies et al., 2018; Toulopoulou et al., 2007). Additionally, findings from analyses of rare variants show that there is an overlap in the rare variant architecture of SCZ and cognitive ability, with many variants known to be associated with SCZ having a negative impact on cognitive function (Chen et al., 2023; Kendall et al., 2019).

GWAS have identified common variants that influence both SCZ risk and general cognitive ability. Using GWAS summary statistics, Smeland et al. (2020a) identified 75 genomic loci that were jointly associated with SCZ and intelligence. Of the 75 shared loci, 81% were found to

increase SCZ risk while being associated with poorer cognitive performance (Smeland et al., 2020a). The identified loci were enriched for genes involved in processes related to neurodevelopment, synaptic integrity, and neurotransmission (Smeland et al., 2020a). An alternative approach to exploring the common genetic determinants of SCZ and cognitive function is through PRS analyses. A recent meta-analysis showed a statistically significant negative association between SCZ-PRS and general cognitive ability in the general population and healthy controls (Mallet et al., 2020). However, the same meta-analysis failed to find a significant relationship between SCZ-PRS and cognitive function in individuals with SCZ (Mallet et al., 2020). In another study, Richards et al. (2020) showed that IQ-PRS and PRS for educational attainment are more strongly predictive of cognitive function in SCZ than SCZ-PRS. Collectively, these findings suggest that the common genetic influences on cognitive dysfunction in SCZ are at least partially distinct from genetic liability for schizophrenia (Mallet et al., 2020; Richards et al., 2020). Additionally, this evidence implies that the same genetic variants that influence cognitive function in the general population contribute, at least in part, to variation in cognitive ability in individuals with SZ (Richards et al., 2020).

At the rare variant level, known SCZ risk CNVs have been associated with cognitive impairment both in the general population and people with SCZ. Within the general population, performance on a range of cognitive tests was worse in SCZ CNV carriers compared to non-carriers (Kendall et al., 2019). In a study conducted in people with SCZ, general cognitive ability was significantly lower, by 0.8 standard deviations, in carriers of SCZ associated CNVs than in non-carriers (Hubbard et al., 2021). Studies of the overlap between rare coding variants for SCZ and cognitive function are scarce but preliminary evidence

suggests that an increased burden of rare damaging mutations is associated with worse cognitive performance in SCZ (Creeth et al., 2022).

Further research is required to delineate variant specific effects on cognitive function and to better understand how the interaction between rare and common variants impacts cognition. A better understanding of the shared genetic determinants between cognitive function and SCZ may facilitate mechanistic insights and the identification of novel therapeutic targets for cognitive impairment in the disorder.

1.4. Study Rationale

Cognitive impairment is an important determinant of functional outcomes in SCZ, however, understanding of the genetic underpinnings of cognitive deficits in the disorder remains incomplete. Most studies exploring the genetic basis of cognitive impairment in SCZ employed global measures of cognitive function, such as general cognitive ability (*g*). We speculate that novel approaches, using alternative metrics of cognitive performance such as WIV, have the potential to further understanding of the biological mechanisms driving cognitive impairment in SCZ. Given that many aspects of WIV in SCZ remain unexplored and there have been no attempts to summarize current knowledge of WIV, this research first sets out to review key literature on clinical, neural and genetic correlates of WIV in SCZ. Next, this thesis contributes to current understanding of the functional and clinical significance of WIV in cognitive performance in SCZ through an exploration of the demographic and clinical determinants of WIV in SCZ in a South African case-control study. Following this, the common genetic determinants of WIV are explored by conducting a GWAS of reaction time variability, an index of across-trial WIV. Finally, this study seeks to gain deeper insights into the shared genetic

architecture of SCZ and cognitive impairment. It will accomplish this by applying novel statistical approaches to data from a large population-based biobank to investigate the genetic overlap between genetically determined factors corresponding to broad cognitive abilities and SCZ. Ultimately, an improved understanding of the genetic basis of cognitive impairment in SCZ may provide new information about the pathways that lead from genes to disease. This knowledge has the potential to facilitate the development of improved diagnostic and therapeutic tools for SCZ.

1.5. Aims and Objectives

The overarching aim of the study is to extend current understanding of cognitive impairment in SCZ by using previously under-researched or novel metrics of cognitive performance.

Table 1. 1: Aims and Objectives of The Thesis

Aim	Objective(s)
1. To characterize individual differences in WIV and its clinical significance in SCZ.	i) Review the key literature on WIV in cognitive performance in SCZ. ii) Explore sex, age and diagnostic group differences in WIV in cognitive performance in individuals with SCZ and healthy controls from the *Genomics of Schizophrenia in the South African Xhosa* (SAX) study. iii) Test for an association between WIV in cognitive performance and functional ability in the SAX cohort.

Aim	Objective(s)
2. To explore the contributions of common genetic variants to WIV, as measured by reaction time variability.	i) Conduct a GWAS of reaction time variability using data from the UK Biobank. ii) Calculate the genetic correlation between reaction time variability and selected neurological and psychiatric traits, including SCZ. iii) Assess whether results from the discovery GWAS replicate in two independent cohorts, the SAX study and *Thematically Organised Psychosis* (TOP) Study, using polygenic risk score analysis.
3. To investigate the overlap in the common genetic underpinnings of cognitive function and SCZ.	i) Conduct univariate GWAS of 12 cognitive traits measured in the UK Biobank. ii) Apply genomic structural equation modelling to derive latent factors underlying the genetic covariance structure among the 12 UK Biobank cognitive traits. iii) Explore the genetic overlap between the latent cognitive factors and SCZ using linkage disequilibrium score regression, Local Analysis of [co]Variant Association (LAVA), bivariate MiXeR, and conjunctional false discovery rate analysis (conjFDR). iv) Investigate the genetic overlap between the latent cognitive factors, schizophrenia and schizophrenia symptom dimensions using polygenic risk score analysis.

The first aim of the thesis is addressed in Chapters 2 and 3, which include peer-reviewed publications that address the research objectives. The second aim of the thesis is addressed

in Chapter 4, which is comprised of a peer-reviewed publication. The work done to fulfil the third aim is discussed in Chapter 5. The final chapter of the thesis, Chapter 6, is dedicated to discussing and synthesizing the results presented in the thesis.

NOTE: Minor adjustments to the format and structure of the original manuscripts have been made in order to maintain thematic consistency and formatting throughout the thesis.

Chapter 2: Literature Review

Within-individual Variability in Cognitive Performance in Schizophrenia

Synopsis

This chapter presents an overview of the key literature on WIV in cognitive performance in people with schizophrenia and addresses objective 1 of this thesis. The review describes current understanding of the clinical, neural, and genetic correlates of WIV in SCZ, identifies key knowledge gaps, and provides directions for future research. This chapter consists of peer reviewed article that was published in *Schizophrenia Research*.

Wootton, O., Dalvie, S., Susser, E., Gur, R. C., & Stein, D. J. (2023). Within-individual variability in cognitive performance in schizophrenia: A narrative review of the key literature and proposed research agenda. Schizophr Res, 252, 329-334.
https://doi.org/10.1016/j.schres.2023.01.028

Authorship Statement

I developed the research question and search strategy for this review with input from my supervisors. I conducted the search and extracted data from the relevant publications. I synthesized the data and wrote the first draft of the manuscript. All co-authors reviewed the draft and provided feedback prior to submission to the journal. I submitted the manuscript to the journal and responded to reviewer feedback with input from the co-authors.

Within-individual Variability in Cognitive Performance in Schizophrenia: A Narrative Review of the Key Literature and Proposed Research Agenda

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2.1. Abstract

Schizophrenia is a neurodevelopmental disorder and a leading cause of disability worldwide. Deficits in cognitive function are characteristic of schizophrenia and are predictors of functional outcomes in the disorder. Within-individual variability (WIV) in cognitive performance is elevated in schizophrenia and has been suggested to provide additional insight into cognitive function over and above mean performance measures. Despite growing interest in WIV in schizophrenia, research on the clinical significance and neural correlates of WIV in the disorder remains sparse. The present narrative review summarizes the key literature linking WIV in schizophrenia to clinical, neural, and genetic correlates. Here, we aim to highlight key knowledge gaps and provide directions for future research into WIV in schizophrenia.

Keywords: schizophrenia; cognition; within-individual variability; reaction time; genetic predisposition to disease; neuroimaging

2.2. Introduction

Impaired cognitive function is a well-documented feature of people with schizophrenia (PSZ) and a major determinant of functional outcomes (Fett et al., 2011; Fioravanti et al., 2012). Typically, mean measures of performance on cognitive tests are used to compare cognitive function between individuals (e.g., distribution among a group) and groups (e.g., people with and without schizophrenia). Studies using such measures have contributed towards our understanding of the neurobiological underpinnings and functional consequences of impaired cognition in PSZ.

Cognitive performance may also be assessed by measuring WIV in performance on cognitive tests. WIV in cognitive functioning reflects the extent of variation in an individual's performance relative to their mean performance across trials of a task, or across multiple tasks in a cognitive battery (MacDonald et al., 2009b). In conditions such as SCZ where variability in performance on cognitive tests is increased, it has been argued that mean measures of performance on one or a battery of tests fail to capture some of the meaningful cognitive differences among people (MacDonald et al., 2009b; Reichenberg et al., 2006; Rentrop et al., 2010). In this context, investigators have suggested that additional insight into cognitive function may be attained by measuring WIV. When performance variability increases, WIV may provide insight into the stability of cognitive processing by capturing systematic as opposed to random errors (MacDonald et al., 2009b).

WIV is increased in PSZ (Cole et al., 2011; Rentrop et al., 2010; Vinogradov et al., 1998), at-risk mental state (ARMs) individuals (Shin et al., 2013) and in family members of PSZ (Roalf et al., 2013a), and there has been increasing interest in its clinical, neural, and genetic correlates.

Despite this growing body of literature, many aspects of WIV in SCZ remain unexplored and there have been no attempts to summarize knowledge of WIV among PSZ. In this narrative review, we aim to provide a brief conceptual overview of WIV, to integrate findings from neuropsychological and neurobiological research into WIV among PSZ and to discuss the implications of these findings for future research.

2.3. Methods

The current literature on WIV in cognitive performance in PSZ was reviewed by searching the PubMeD, Scopus, Web of Science and PsycInfo databases (last search: 30 September 2022). We used the following search terms: “("Within-individual variability" OR "Intra-individual variability" OR WIV OR IIV OR "Cognitive variability" OR “reaction time variability” OR “behavioural variability” OR “intraindividual differences”) AND (cognit* OR “neuropsychological tests”) AND (Schizophrenia OR Psychosis OR Psychotic disorder" OR “at-risk mental state” OR “psychotic disorder not otherwise specified” OR “schizophreniform disorder” OR “brief psychotic episode”)”. This yielded 114 records after duplicates were removed. Titles and abstracts were screened to determine eligibility and 43 articles reached inclusion criteria for consideration in this review. Cross-referencing of the relevant articles was also performed. Studies were included if they were published in English and measured WIV in cognitive performance in PSZ, people with psychotic spectrum disorders, or people at risk of developing SCZ. Studies were excluded if the full text article was not available.

2.4. Within-individual Variability: Background

WIV has been widely studied in cognitive aging and is characterized by a U-shaped function across the lifespan; decreasing throughout childhood and adolescence before increasing

throughout adulthood (Hultsch et al., 2002; MacDonald et al., 2009b; Roalf et al., 2014a). It is hypothesized that the characteristic changes to brain structure that occur during neurodevelopment and thereafter are responsible for the observed changes in WIV over the lifespan (MacDonald et al., 2006). Additionally, sex differences in WIV have been demonstrated with males having increased WIV in cognitive performance compared to females (Roalf et al., 2014a). Variability in cognitive performance is present in healthy adults (Binder et al., 2009), however when variability exceeds a certain threshold, it is a useful indicator of impaired cognitive function (MacDonald et al., 2009b). Increased WIV has been consistently associated with SCZ, traumatic brain injury, major neurocognitive disorders and attention deficit hyperactivity disorder (ADHD) (Cole et al., 2011; Leth-Steensen et al., 2000; Lin et al., 2015; MacDonald et al., 2009b; Roalf et al., 2013b; Stuss et al., 2003).

WIV may be operationalized in 3 ways: i) across-tasks in the same testing session, ii) across trials of the same task during the same testing session, and iii) across trials of the same task during different testing sessions (Cole et al., 2011; MacDonald et al., 2009b). This review will focus on the first two measures of WIV, which are measured over short time periods, and are thought to better capture endogenous processes, such as abnormal neural activity (MacDonald et al., 2009b). In conditions such as SCZ, where performance across cognitive domains is differentially affected, across-task WIV may be used to differentiate PSZ from matched controls (Cole et al., 2011; Roalf et al., 2013a; Roalf et al., 2013b). However, it is more common for studies of WIV to calculate across-trial WIV using reaction times for correct trials of a cognitive task (MacDonald et al., 2009b). Standard measures of across-trial reaction time variability (RTV) include the individual standard deviation and the individual coefficient of variation. The individual coefficient of variation is calculated as the ratio of the individual

standard deviation to the individual's mean reaction time (Stuss et al., 2003). Whereas the individual standard deviation may be higher in individuals with longer but not necessarily more variable reaction times, the individual coefficient of variation is robust to these effects and is considered a more reliable measure of WIV (Stuss et al., 2003). Standard methods of measuring RTV have been criticized as reaction time distributions are typically positively skewed with a higher proportion of longer reaction times and thus, are not accurately represented by a normal distribution (see **Figure 2.1**). A newer approach to the analysis of WIV involves applying an ex-Gaussian model to the reaction time distributions (Leth-Steensen et al., 2000; Rentrop et al., 2010). The ex-Gaussian distribution can be decomposed into two independent components: a normal component, and an exponential component, which corresponds to the right-sided tail of the distribution (Heathcote et al., 1991; Luce, 1986). The mean of the exponential component (tau) is used as a measure of RTV with a larger tau corresponding to an increase in variability of reaction times (Heathcote et al., 1991).

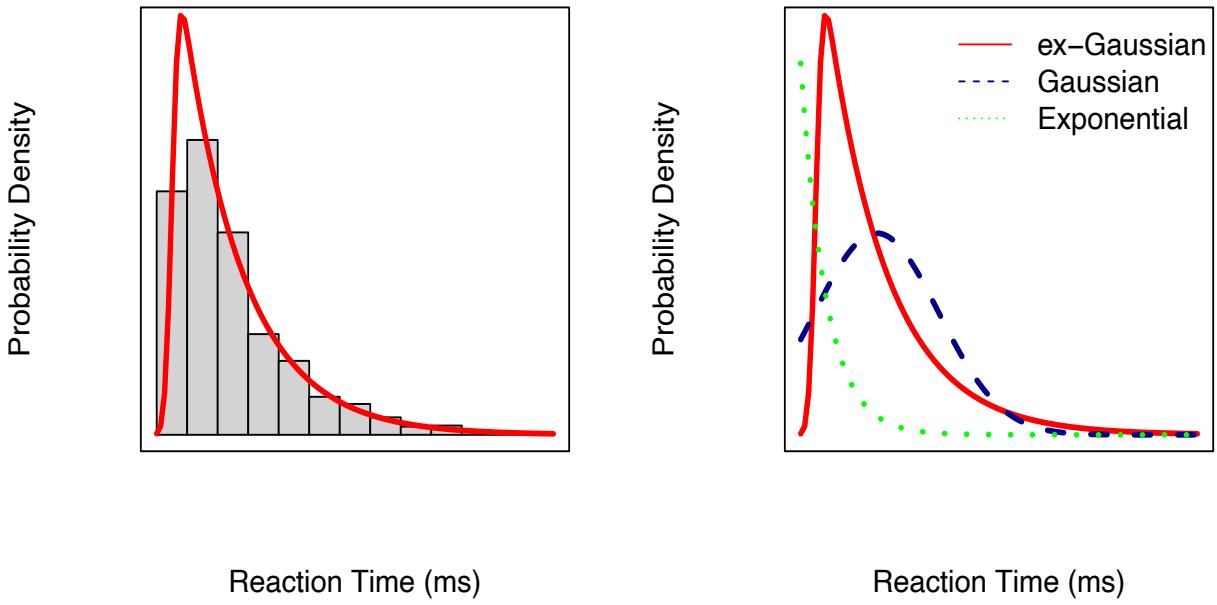

Figure 2. 1: Reaction Time Distributions.

A. Typical positively skewed reaction time distribution illustrated with simulated data. **B**. Ex-gaussian distribution illustrated with exponential and gaussian components. Three measurements may be obtained from the ex-Gaussian distribution: the mean (mu) of the normal component, the standard deviation (sigma) of the normal component, and the mean (tau) of the exponential component

2.5. The Functional and Clinical Significance of WIV in Schizophrenia

Variability in task performance has been documented as a feature of SCZ since Kraepelin's seminal works on dementia praecox (Kraepelin, 1913). Over the past century, efforts have been made to understand the utility of WIV as a risk factor for psychosis and its relationship with symptom severity and functional outcomes. There is mounting evidence that WIV may be an early indicator of susceptibility to psychosis. In ARMS individuals, increased across-trial WIV on a reaction time task has been demonstrated when mean performance measures on cognitive tests were within normal range (Shin et al., 2013). Further, elevated WIV has been

found to be predictor of psychopathology in healthy population cohorts. A large population-based longitudinal study found that elevated across-trial WIV in reaction time in adolescence was predictive of later psychotic-like experiences (Wallace & Linscott, 2018). Additionally, increased across-task WIV in adolescents with normal intelligence quotient (IQ) scores was found to be associated with an increased risk of later hospitalization for SCZ (Reichenberg et al., 2006). As elevated WIV has been observed in youth with ADHD and mood disorders, it is unlikely that it is specific to risk of psychosis (Doyle et al., 2018). Instead, WIV appears to represent a disruption to cognitive processes arising from neurobiological abnormalities that are common across neurodevelopmental disorders (Wallace & Linscott, 2018).

PSZ demonstrate deficits across multiple cognitive domains when compared to matched controls (Fioravanti et al., 2012; Heinrichs & Zakzanis, 1998). This global deficit in cognitive function is typically captured by *g,* a measure of general cognitive ability. In PSZ, *g* and across-task WIV in cognitive performance are negatively correlated (Cole et al., 2011) however, it has been proposed that WIV is a more sensitive marker of cognitive deficits. In a study of high-functioning PSZ, across-task WIV significantly differed between PSZ and healthy controls when premorbid IQ and mean performance measures on cognitive tasks did not (Rentrop et al., 2010). Despite the utility of WIV as an index of impaired cognition in SCZ, its clinical and functional significance in the disorder remains unclear. Studies have failed to show a consistent relationship between WIV and negative, positive, and disorganized symptoms in PSZ (Akiyama et al., 2016; Pellizzer & Stephane, 2007; Rentrop et al., 2010; Roalf et al., 2013b; Shin et al., 2013; Wexler et al., 2004). **Table 2.1.** provides an overview of key findings from studies assessing the relationship between WIV and symptom severity in PSZ. The heterogeneity in results may be attributed to the different measures of WIV and symptom

severity across studies. Alternatively, it is possible that the neural mechanisms responsible for increased WIV in PSZ differ from those underlying the other symptom domains. Findings regarding the association between WIV and functional ability in PSZ are more consistent. For example, multiple studies have shown a negative correlation between across-trial WIV in reaction time and measures of functional ability, including occupational and global functioning (Rentrop et al., 2010; Vinogradov et al., 1998; Wexler et al., 2004). To extend this knowledge, future research may consider the use of longitudinal studies to explore the utility of WIV as a predictor of functional outcomes.

Table 2. 1: Overview of Studies Assessing the Relationship Between Cognitive Variability and Symptom Severity in People with Schizophrenia

Article	*N*	Study Design	Cognitive Assessment	Measure of Cognitive Variability	Measure of Symptom Severity	Main Findings
Akiyama et al. (2016)	PSZ (*n* = 288) HC (*n* = 308)	Cross-sectional	Brief Assessment of Cognition in Schizophrenia	Within-individual standard deviation of performance on cognitive tests	PANSS	Significant negative relationship between WIV and negative symptom score. No association between WIV and scores on positive or general psychopathology subscales.
Pellizzer and Stephane (2007)	PSZ (*n* = 21) HC (*n* = 18)	Cross-sectional	Choice RT Task	Within-individual inter-quartile range of reaction time across correct trials	BPRS SAPS SANS	No significant relationship between WIV and symptom score.
Rentrop et al. (2010)	PSZ (*n* = 28) HC (*n* = 28)	Cross-sectional	Go/Nogo task Continuous Performance Test	Ex-gaussian parameters for correct responses in the Frequent-Go condition in Go/Nogo task	PANSS	No significant relationship between ex-gaussian parameters and symptom scores.
Roalf et al. (2013b)	PSZ (*n* = 25) HC (*n* = 27)	Cross-sectional	University of Pennsylvania Computerized Neurocognitive Battery	Within-individual standard deviation of speed and accuracy performance measures across cognitive tests	BPRS SAPS SANS	Increased speed WIV was associated with higher SAPS scores. No association between speed WIV and SANS or BPRS. No association between accuracy WIV and symptom measures.

Article	*N*	Study Design	Cognitive Assessment	Measure of Cognitive Variability	Measure of Symptom Severity	Main Findings
Shin et al. (2013)	PSZ (*n* = 37) HC (*n* = 38) ARMS (*n* = 27)	Cross Sectional	Stop-signal task from the Cambridge Computerized Neuropsychological Tests	Within-individual standard deviation of speed and performance measures across sub-blocks of the SST	PANSS BPRS	Trend level positive correlation between WIV in the stop process in PSZ and general psychopathology scores on the PANSS. No association between WIV and negative and positive symptom scores.
Wexler et al. (2004)	PSZ (*n* = 17)	Longitudinal	10 visual or auditory discrimination tasks from Psychological Software Services	Within-individual coefficient of variation in reaction time across trials	PANSS	No association between WIV and symptom scores.

Note. This table provides an an overview of key findings from studies assessing the relationship between WIV and symptom severity in PSZ. ARMS, at-risk mental state; BPRS, Brief Psychiatric Rating Scale; HC, healthy control; PANSS, Positive and Negative Syndrome Scale; PSZ, people with schizophrenia; RT, reaction time; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; SST, stop-signal task; WIV, within-individual variability

2.6. The Neural Correlates of WIV in Schizophrenia

It has been suggested that disruptions in brain white matter underlie increased WIV in PSZ. White matter tracts that have been associated with elevated across-task WIV in the disorder include the cingulum bundle, inferior frontal fasciculus (Roalf et al., 2013b), and corpus callosum (Ahn et al., 2019). Roalf and colleagues (2013) found that fractional anisotropy was reduced in bilateral frontal, temporal, and occipital white matter in PSZ compared to healthy controls but that in these regions, only fractional anisotropy in the cingulum bundle and inferior frontal fasciculus was associated with WIV.

Abnormalities of cingulum bundle white matter have been associated with impaired performance in the cognitive domains of attention (Nestor et al., 2007), executive function (Tyburski et al., 2020) and visual memory (Nestor et al., 2008) whereas disruptions of the inferior frontal fasciculus are associated with impaired semantic processing (Duffau et al., 2005; Moritz-Gasser et al., 2013) and emotion processing (Philippi et al., 2009). While it is possible that disrupted white matter integrity in the cingulum bundle and inferior frontal fasciculus is responsible for increased WIV in PSZ, further studies are required to determine if this relationship is causal as the observed white matter changes may be a consequence of structural abnormalities in other regions of the brain. Although Roalf et al. (2013) observed reduced fractional anisotropy in the corpus callosum in PSZ compared to healthy controls, they did not find an association between the corpus callosum and WIV. A study by Ahn et al. (2019) focused on fractional anisotropy in the corpus callosum in PSZ and found that reduced fractional anisotropy in the genu of the corpus callosum was associated with elevated WIV. The genu of the corpus callosum is involved in the interhemispheric transfer and integration of information between the anterior cerebral hemispheres and prefrontal cortex (Anstey et

al., 2007). Ahn et al (2017) hypothesized that abnormalities of this region may result in abnormal performance on neurocognitive tasks that require prefrontal input, thus increasing variability in performance across neurocognitive domains.

Electroencephalography and functional magnetic resonance imaging have been used to study the relationship between WIV in cognitive performance and neural activity. Decreased activation of the dorsolateral prefrontal cortex has been associated with periods of increased across-trial WIV in reaction time in PSZ (Fassbender et al., 2014; Panagiotaropoulou et al., 2019). Hypoactivity of the dorsolateral prefrontal cortex has been linked to deficits in inhibitory control in PSZ (Rubia et al., 2001; Yoon et al., 2008), and it has been suggested that the associated reduction in cognitive stability is indexed by an increase in WIV. To better understand the abnormalities in cognitive control in PSZ, studies have explored the relationship between WIV in cognitive performance and event-related oscillations in the EEG spectra. Chidharom et al. (2021) observed that impairment of frontal midline theta phase coherence was associated with periods of increased across-trial WIV in reaction time in a Go/NoGo task in PSZ. These results are consistent with findings of lower theta inter-trial coherence during periods of increased WIV in reaction time in people with ADHD and healthy controls (Groom et al., 2010; Papenberg et al., 2013). Previous research suggests that theta band activity is a neural correlate of cognitive control processes mediated by the medial frontal cortex (Cohen et al., 2008; Wang et al., 2005). Theta band phase inter-trial coherence is hypothesized to represent the engagement of task-relevant brain regions by the medial frontal cortex (Cavanagh et al., 2009). Thus, it is possible that one mechanism underlying increased WIV in PSZ is impaired engagement of the cognitive control network. Further, Kang et al. (2019) used event-related potentials to link across-trial WIV in reaction time to impaired

cognitive control in context processing in PSZ. This study provided evidence that increased across-trial RTV is related to deficits in pre-frontal motor coordination for reactive control in PSZ. Additionally, it was found that WIV was increased during trials with lower cognitive demands. Kang et al. (2019) hypothesize that WIV in PSZ is not only due to deficits in prefrontal motor control but that PSZ fail to suppress default mode network activity during easier trials, resulting in a further increase in variability.

Research relating WIV to changes in neurotransmitters and activity across functional networks has been conducted in healthy populations but, to our knowledge, no studies have examined these neural correlates of WIV in PSZ. Altered dopaminergic and cholinergic activity in the brain has been associated with increased behavioural WIV (MacDonald et al., 2009a; MacDonald et al., 2009b). Although altered dopaminergic activity is present in SCZ, no research has directly explored the relationship between dopaminergic neurotransmission and WIV in cognitive performance in this population. Similarly, impaired regulation and coordination of the default mode and task-positive networks have been associated with an increase in behavioural WIV (Kelly et al., 2008). Disrupted default mode network activity has been observed in PSZ, however further research is required to determine the extent to which this contributes to WIV in cognitive performance in this disorder.

2.7. Genetics of WIV in Schizophrenia

The genetic basis of WIV in cognitive performance remains unclear. There is evidence to suggest that WIV may vary in relation to genetic susceptibility for SCZ. Two large studies found that across-task WIV on a neurocognitive test battery significantly differed between PSZ, their unaffected family members, and healthy individuals (Cole et al., 2011; Roalf et al., 2013a).

Both studies found that PSZ had higher WIV than their unaffected relatives, who showed increased WIV compared to healthy individuals. Contrastingly, studies comparing across-trial WIV in reaction times on a sustained attention task in PSZ, their family members and healthy individuals failed to find a difference between WIV in family members and healthy individuals (Birkett et al., 2007; Hilti et al., 2010). One possible explanation for this inconsistency is that genetic susceptibility to SCZ is unrelated to the deficits in attentional control indexed by RTV. Future work should attempt to understand the neuropsychological domains that contribute to increased WIV in those with a genetic predisposition to SCZ.

To date, the genetic basis of WIV in cognitive performance has only been investigated using a candidate gene approach. A common polymorphism (Val158Met- rs4680) in the gene encoding for the enzyme, catechol-O-methyltransferase (COMT), has been associated with differences in measures of behavioural WIV; however, findings have been inconsistent. (Craddock et al., 2006). The Val allele has shown to be associated with a significant increase in enzymatic activity and more rapid degradation of dopamine in the prefrontal cortex (Craddock et al., 2006). It is hypothesized that the subsequent reduction in dopamine signaling results in impaired performance on frontally mediated cognitive tasks (Craddock et al., 2006). Results from studies investigating the relationship between the COMT genotype and WIV have been inconsistent. In healthy controls, increased Val loading has been associated with increased RTV during a continuous performance test (Stefanis et al., 2005), and with higher RTV for unfamiliar faces in a facial recognition task (Rostami et al., 2017). Contrastingly, Salunkhe et al. (2019) found that increased Met loading was associated with increased RTV for a working memory task in healthy adults and Krabbendam et al. (2006) showed that the Met allele was associated with increased RTV on a continuous performance

test for PSZ, their first degree relatives, and healthy controls. Differences in sample characteristics as well cognitive measures may have contributed to the inconsistencies among study results. Additionally, it is likely that the effect of the COMT genotype on frontal lobe function is more nuanced than previously hypothesized (Craddock et al., 2006).

Given the limitations of the candidate gene approach and advances in molecular genetics, future research on the genetic basis of WIV in cognitive performance should consider a genome-wide approach. Research has proven that complex traits, such as cognitive ability, are generally polygenic in nature with many genes across the genome contributing to the phenotype (Davies et al., 2018). A well-powered genome-wide investigation of the genes associated with WIV in cognitive performance would allow for identification of novel genetic loci. Results from a GWAS of WIV may inform our understanding of the biological pathways contributing to impaired cognitive performance in conditions such as SCZ.

2.8. Conclusions and Recommendations

In this narrative review, we have summarized the literature on the clinical, neural, and genetic correlates of WIV in cognitive performance in PSZ. WIV in PSZ may have multiple origins and has been associated with abnormal white matter integrity, functional connectivity, and dopaminergic activity in the disorder. Although WIV is non-specific to PSZ, elevations in WIV appear to be a sensitive indicator of psychopathology even when mean performance measures on cognitive tests are normal. WIV is relatively easy to measure and may be calculated from pre-existing datasets. This feature may further add to its utility as a predictor of psychosis risk in healthy populations and of functional outcomes in people with psychosis.

Further, the relative ease of measurement of WIV makes it an attractive phenotype for large GWAS.

Despite progress in our understanding of WIV in cognitive performance in PSZ, several key questions remain unanswered. First, the relationship between WIV and symptoms of SCZ is unclear. This may be due to heterogeneity of study designs and differences in measurements of WIV and symptom severity. The comparability of WIV and symptom severity measures across studies should be considered when planning future research in this area. An improved understanding of the relationship between WIV and symptom domains in PSZ may provide insight into the extent to which the neurobiological underpinnings of the symptoms of SCZ overlap or differ.

Second, although the neural basis of WIV has been explored using a number of brain imaging techniques, certain potential neural correlates of WIV are yet to be examined. Abnormalities in brain structural volumes are well described in PSZ (Kuo & Pogue-Geile, 2019) but the extent to which these relate to WIV in the disorder has not been studied. Similarly, disrupted functional network connectivity and abnormal dopaminergic activity are present in PSZ but their relationship to WIV in this disorder remains unexplored. Additionally, it is likely that multiple neural mechanisms contribute to increased WIV in SCZ and multi-modal neuro-imaging studies may be best suited to explore this interaction.

Third, evidence suggests that there may be a genetic basis for WIV in cognitive performance. Progress in molecular genetics and the formation of large genetic data consortia provide an opportunity to apply a genome-wide approach to discover genes associated with WIV. The

discovery of genetic loci associated with WIV may provide further information about the biological processes contributing to impaired cognition in PSZ and ultimately, facilitate the discovery of novel therapeutic targets.

In closing, WIV may provide additional insight into cognitive function in PSZ over and above mean performance measures. Research on WIV in PSZ has the potential to heighten our understanding of the neurobiological disruptions that characterize the disorder. This knowledge may inform treatment strategies for SCZ as well as strategies to predict and mitigate risk of psychosis.

Chapter 3: Original Research Article 1

Predictors of Within-Individual Variability in Cognitive Performance in Schizophrenia in a South African Case-Control Study

Synopsis

This chapter addresses objectives 2 and 3 of this thesis and includes an investigation of the demographic and clinical correlates of WIV in cognitive performance in a large study of people with schizophrenia and matched controls in South Africa. The basis of this chapter is an original research article published in *Acta Neuropsychiatrica*.

Wootton, O., Dalvie, S., MacGinty, R., Ngqengelele, L., Susser, E. S., Gur, R. C., & Stein, D. J. (2023). Predictors of within-individual variability in cognitive performance in schizophrenia in a South African case–control study. *Acta Neuropsychiatrica*, 1-7. https://doi.org/10.1017/neu.2023.28

Authorship Statement

I conceptualized the research question and formulated the objectives for this secondary data analysis with guidance from my supervisors. I performed the data analysis with input from R MacGinty and RC Gur. I wrote the first draft of the manuscript. All co-authors provided commentary and contributed to subsequent revisions of the manuscript. I submitted the manuscript to the journal and responded to reviewer feedback. All co-authors approved the final version of the manuscript.

Predictors of within-individual variability in cognitive performance in schizophrenia in a South African case-control study

Running Title: Predictors of WIV in Schizophrenia

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3.1. Abstract

Introduction: Cognitive dysfunction in schizophrenia may be assessed by measuring within-individual variability (WIV) in performance across a range of cognitive tests. Previous studies have found increased WIV in people with schizophrenia, but no studies have been conducted in low to middle income countries where the different sociocultural context may-affect WIV. We sought to address this gap by exploring the relationship between WIV and a range of clinical and demographic variables in a large study of people with schizophrenia and matched controls in South Africa.

Methods: 544 people with schizophrenia and 861 matched controls completed an adapted version of The University of Pennsylvania Computerized Neurocognitive Battery (PennCNB). Demographic and clinical information was collected using the Structured Clinical Interview for DSM-IV Diagnoses. Across-task WIV for performance speed and accuracy on the PennCNB was calculated. Multi-variate linear regression was used to assess the relationship between WIV and a diagnosis of schizophrenia in the whole sample; and WIV and selected demographic and clinical variables in people with schizophrenia.

Results: Increased WIV of performance speed across cognitive tests was significantly associated with a diagnosis of schizophrenia. In people with schizophrenia, increased speed WIV was associated with older age, a lower level of education, and a lower score on the global assessment of functioning scale. Increased accuracy WIV was significantly associated with a younger age in people with schizophrenia.

Conclusions: Measurements of WIV of performance speed can add to the knowledge gained from studies of cognitive dysfunction in schizophrenia in resource limited settings.

Keywords: schizophrenia/cognition disorders/neuropsychological tests/humans/within-individual variability.

Significant Outcomes	Increased WIV across speed measures was associated with schizophrenia and poorer functional outcomes in the disorder, while no such effects were observed for WIV in accuracy. This finding provides support for the use of measures of speed WIV in future studies exploring the biological basis of cognitive dysfunction in schizophrenia.
	The finding of a negative relationship between speed WIV and educational attainment provides further evidence for the positive association between years of education and cognitive function, whether measured by WIV or another metric.
Limitations	There were substantially more males than females in this cohort, which made accurate assessment of the relationship between sex and WIV challenging.
	A detailed rating scale was not used to assess symptom severity in schizophrenia which may have limited the analysis of the relationship between symptom severity and WIV.

3.2. Introduction

Cognitive dysfunction is characteristic of SCZ (Cole et al., 2011; Rentrop et al., 2010; Roalf et al., 2013a; Saykin et al., 1991; Vinogradov et al., 1998). WIV in cognitive functioning reflects the extent of the variation in an individual's performance relative to their mean performance, and it has been suggested that WIV provides additional insight into cognitive function over and above mean-based performance measures (MacDonald et al., 2009b; Roalf et al., 2013a). WIV indexes risk of psychosis in the general population and is a predictor of functional outcomes in SCZ (Reichenberg et al., 2006; Shin et al., 2013; Vinogradov et al., 1998; Wallace & Linscott, 2018; Wexler et al., 2004). Additionally, elevations in WIV have been observed in individuals with high risk of developing psychosis when mean measures of performance are normal (Shin et al., 2013).

WIV may be operationalized in 3 ways: 1) across-tasks in the same testing session, 2) across trials of the same task during the same testing session, and 3) across trials of the same task during different testing sessions (Cole et al., 2011; MacDonald et al., 2009b). Across-trials and across-task WIV are positively correlated (Hultsch et al., 2002) and elevations in both measures of WIV have been demonstrated in PSZ (Cole et al., 2011; Fassbender et al., 2014; Reichenberg et al., 2006; Roalf et al., 2013a). Although it is typical to calculate WIV using measures of performance speed, WIV for performance accuracy may also be used to assess cognitive function (MacDonald et al., 2009b; Roalf et al., 2013a; Roalf et al., 2014a). Previous studies have found elevated across-task WIV for performance speed and accuracy in PSZ, reflecting an inability to maintain performance across tasks assessing different neurocognitive domains (Roalf et al., 2013a; Roalf et al., 2013b). Although the neural correlates of WIV require further research, abnormalities of brain white matter and hypoactivity of the

dorsolateral prefrontal cortex have been associated with elevated WIV in SCZ (Ahn et al., 2019; Fassbender et al., 2014; Panagiotaropoulou et al., 2019; Roalf et al., 2013b). Increased WIV has also been demonstrated in disorders such as ADHD (Leth-Steensen et al., 2000; Lin et al., 2015), traumatic brain injury (Stuss et al., 2003), and dementia (Halliday et al., 2018; Holtzer et al., 2008; Webber et al., 2022), including HIV-associated neurocognitive disorder (Vance et al., 2021). Further, factors such as ageing, male sex and lower level of education have been associated with increased WIV (Cole et al., 2011; De Felice & Holland, 2018; Hilborn et al., 2009; Roalf et al., 2014a).

Despite increasing interest in WIV as a measure of cognitive dysfunction, it has only been studied in a limited number of settings. To our knowledge, no studies of WIV in SCZ have been conducted in LMICs where differences in educational levels, the prevalence of comorbid conditions (such as HIV), and treatment practices may affect the relationship between WIV and specific disorders. To promote the development of contextually relevant diagnostic and treatment practices, there is a need to assess the generalizability of findings from neuropsychological research on SCZ from high-income settings to other contexts. Additionally, the association between symptom severity and WIV in SCZ remains unclear as results have been inconsistent with some studies finding a positive association and others finding no relationship (Akiyama et al., 2016; Pellizzer & Stephane, 2007; Rentrop et al., 2010; Roalf et al., 2013b; Shin et al., 2013; Wexler et al., 2004).

Here, we aim to address a gap in current knowledge by examining the relationship between across-task WIV and SCZ in a large case-control study from South Africa. Data was originally collected for a genetic study on SCZ but includes information on a range of cognitive,

demographic, and clinical variables. Thus, the study is uniquely placed to explore the relationship between 1) WIV and SCZ, 2) WIV and demographic variables (age, sex, and level of education), and 3) WIV and clinical variables (HIV status, substance use, symptom severity, and functional outcomes) in a LMIC.

3.3. Materials and Methods

3.3.1. Participants

PSZ and matched controls underwent neuropsychological testing as part of the Genomics of Schizophrenia in the South African Xhosa people (SAX) study (Gulsuner et al., 2020). The SAX study is a case-control study that aimed to identify genetic variants and social exposures contributing to SCZ risk in the Xhosa population of South Africa. The Xhosa people are one of the largest black African groups in South Africa and live primarily in the Eastern and Western Cape provinces of the country. The SAX study enrolled 2,849 individuals that self-identified as Xhosa from community healthcare clinics and psychiatric hospitals in the Western and Eastern Cape of South Africa between January 2013 and February 2018. Eligible cases were individuals aged 21-60 years with a diagnosis of SCZ or schizoaffective disorder for at least 2 years, with the capacity to provide informed consent for the genomics study. Controls were matched to cases for age, sex and level of education and were individuals presenting to the same community healthcare clinics as cases for non-psychiatric medical conditions.

3.3.2. Instruments and measures

A translated Xhosa language version of the Structured Diagnostic Interview for DSM-IV Axis I Disorders (SCID-I) (First & Gibbon, 2004) was administered to all study participants by trained psychiatric nurses. The non-patient version of the SCID-I was administered to controls to

screen for psychotic symptoms. As previously reported, inter-rater reliability for the Xhosa version of the SCID-I was adequate for the principle psychotic disorder ($\kappa = 0.74$, $p < .001$) (Mall et al., 2020). Where possible, information from medical records, family members and healthcare professionals was incorporated and considered in the diagnostic process. Global functioning was assessed using the Global Assessment of Functioning Scale (GAF) (Aas, 2011).

An adapted 10-test version of the PennCNB was administered to 544 cases and 861 controls (n = 1,405) in isiXhosa. The PennCNB is designed to assess cognitive domains related to underlying brain networks through the application of "neurobehavioral probes" that have been validated with functional neuroimaging (Gur et al., 1992; Roalf et al., 2014b). The PennCNB has demonstrated adequate psychometric properties in a number of settings (Gur et al., 2001; Gur et al., 2010; Moore et al., 2015; Scott et al., 2021; Service et al., 2020), and evidence for the validity of the Xhosa version of the CNB is presented in Scott et al. (2021). The tests included in the Xhosa version of the battery were designed to measure domains of neurocognition and social cognition that are known to be affected in SCZ (Scott et al., 2021). Descriptions of the English versions of the tests have been published. Briefly, the Xhosa version of the battery assesses five neurocognitive domains: 1) executive function, 2) episodic memory, 3) complex cognition, 4) social cognition, and 5) sensorimotor speed. **Table 3.1.** lists the 10 tests included in the Xhosa version of the battery and the neurocognitive domains that they are designed to assess. Measures of speed and accuracy are calculated for each test except for the Motor Praxis Test and Computerized Finger Tapping Test for which only a measure of speed is obtained.

Table 3. 1: Neurocognitive Domains and Tests Included in the Xhosa Version of the PennCNB

Neurobehavioural Function	Domain	Test
Executive-Control	Abstraction/flexibility	Penn Conditional Exclusion Test
	Attention	Penn Continuous Performance Test
	Working Memory	Fractal N-Back
Episodic Memory	Face Memory	Penn Face Memory
	Spatial Memory	Visual Object Learning Test
Complex Cognition	Non-verbal Reasoning	Penn Matrix Reasoning Test
	Line Orientation	Penn Line Orientation Test
Social Cognition	Emotion Identification	Penn Emotion Recognition Test
Sensorimotor	Sensorimotor Speed	Motor Praxis Test
	Motor Speed	Computerized Finger Tapping Test

3.3.3. Ethics

All participants provided signed informed consent. To assess capacity to consent, The University of California, San Diego Brief Assessment of Capacity to Consent Questionnaire (UBACC) was administered to all participants (Campbell et al., 2017; Jeste et al., 2007). The study was approved by the University of Cape Town Human Research Ethics Committee (reference number – 049/2013).

3.3.4. Data analysis

Demographic and clinical characteristics of the cases and controls that completed the PennCNB were compared using t-tests and Pearson chi-square tests for continuous and categorical variables respectively. An index of across-task WIV was calculated for each participant who completed five or more cognitive tests (*n* = 1,088) using methodology described in previous studies (Holtzer et al., 2008; Roalf et al., 2013b). First, speed and accuracy measures for each test were *z*-transformed based on the distribution of the entire sample. Second, across-task WIV for both speed and accuracy was calculated using the following equation:

$$\mathrm{WIV} = \sqrt{\sum_{k=1}^{K} \frac{(Z_{ik} - A_i)^2}{(K-1)}}$$

where Z_{ik} is the *k*th test score for the *i*th individual and:

$$A_i = \sum_{k=1}^{K} \frac{Z_{ik}}{K}$$

is the individual's mean *z*-transformed test score based on all completed cognitive tests in a battery.

For both speed and accuracy WIV, the data were skewed to the right and heteroscedasticity was present. WIV was log transformed to an approximately normal distribution, and the natural log of WIV was taken as the dependent variable in further analyses. First, the relationship between a diagnosis of SCZ and speed and accuracy WIV was assessed using

multivariate linear regression in the whole sample. Age, sex, level of education, case-control status, human immunodeficiency virus (HIV) status, and history of substance use were included as covariates in the analysis. Second, multivariate linear regression was conducted using cases only with WIV as a dependent variable and age, sex, level of education, HIV status, history of substance use, GAF score, and symptom severity as independent variables. All statistical analyses were performed using IBM SPSS version 28.0.1.0.

3.4. Results

3.4.1. Sample characteristics

Of the cases, 96.5% (n = 525) had a principal axis 1 diagnosis of SCZ. The term SCZ will be used to describe the diagnosis of all cases in the remainder of the text. The demographic and clinical characteristics of the sample are summarized in **Table 3.2**. Controls were significantly younger than cases (p = .004). Level of education and sex did not differ significantly between the two groups. There was a significantly higher number of controls with a diagnosis of HIV (p < .001). Street drug use differed significantly between the two groups with a higher number of cases reporting a history of street drug use (p < .001). Scores on the GAF were significantly higher amongst controls (p < .001).

3.4.2. Within-individual variability and schizophrenia

WIV for accuracy and speed measures on the PennCNB is presented in **Figure 3.1**. A multivariate linear regression was used to assess the relationship between WIV for speed and accuracy measures on the PennCNB and a diagnosis of SCZ in the entire sample. There was a significant relationship between speed WIV and a diagnosis of SCZ (β = 0.255, p < .001), but

there was no significant relationship between accuracy WIV and a diagnosis of SCZ (β = 0.021, *p* = .51).

3.4.3. Predictors of Within-individual variability in schizophrenia

Amongst cases, speed WIV was significantly associated with age, level of education, and GAF (**Table 3.3**). There was a negative association between level of education and speed WIV, (β = - 0.11, *p* = .035). A higher GAF score was associated with a lower speed WIV (β = - 0.17, *p* = .002). Symptom severity, substance use, HIV status, and sex, did not have a significant relationship with speed WIV. Age was positively correlated with WIV for speed (β = 0.22, *p* < .001), but contrastingly was negatively correlated with WIV for accuracy (β = - 0.13, *p* = .022). Age was the only significant predictor of accuracy WIV in PSZ (**Table 3.4**).

Table 3. 2: Sample Demographic and Clinical Characteristics (N = 1,405)

	Controls (*n* = 861)	Cases (*n* = 544)	*P*-value
Age, years (SD)	36.48 (9.10)	35.02 (9.36)	0.004**
Sex, (%)			0.748
Male	780 (90.59)	490 (90.07)	
Years of Education (*%*)			0.085
≤7	248 (28.97)	128 (23.62)	
8-11	449 (52.45)	292 (53.87)	
12	92 (10.79)	66 (12.81)	
>12	67 (7.83)	56 (10.33)	
HIV Status (*%*)			<0.001***
Positive	132 (15.33)	24 (4.41)	
History of Street Drug Use (*%*)			<0.001***
Yes	159 (18.88)	246 (46.24)	
GAF Score (SD)	71.11 (12.53)	59.06 (10.00)	<0.001***
Symptom Severity			
No Symptoms	--	29 (5.98)	
Mild	--	71 (14.64)	
Moderate	--	382 (78.76)	
Severe	--	3 (0.62)	

Note. GAF Global Assessment of Functioning Scale, *HIV* human immune-deficiency virus

*p<0.05, **p<0.01, ***p<0.001

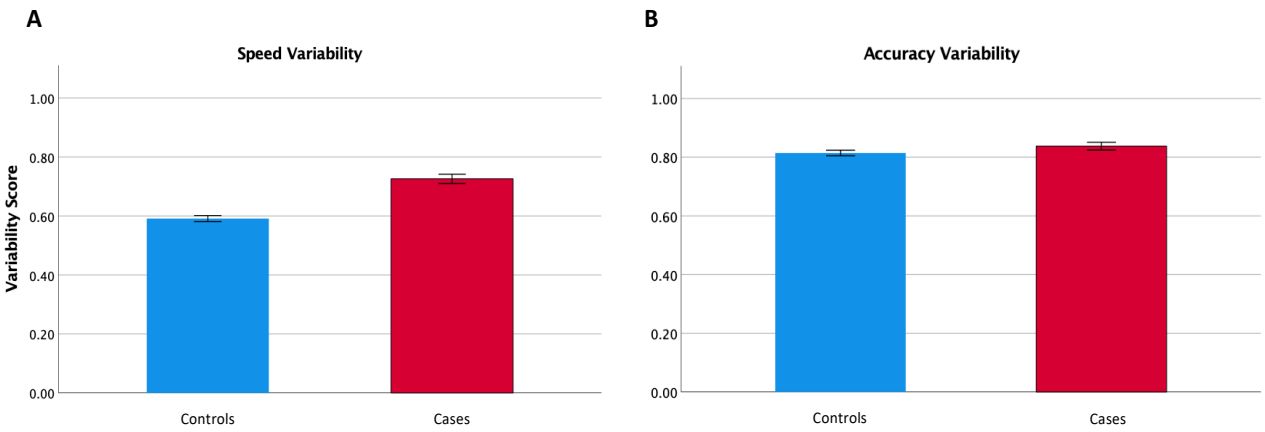

Figure 3. 1: Means (+ standard error of the mean) for Across-task Within-individual Variability for Speed and Accuracy in Matched Controls and People with Schizophrenia

Higher variability scores are indicative of worse overall performance.

Table 3. 3: Linear Regression Analysis of Selected Predictor Variables and WIV-Speed Amongst People with Schizophrenia (n = 353)

Predictor Variable	B	95% CI	β	*p*
Age	0.011	[0.006, 0.016]	0.221	< 0.001***
Sex	-0.022	[-0.191, 0.147]	-0.014	0.797
Education	-0.047	[-0.091, -0.003]	-0.111	0.035*
HIV Status	-0.005	[-0.233, 0.224]	-0.002	0.969
Substance Use	-0.046	[-0.095, 0.004]	-0.098	0.069
Symptom Severity	0.067	[-0.011, 0.145]	0.087	0.093
GAF	-0.008	[-0.013, -0.003]	-0.166	0.002**
Constant = -0.159 , $F(7,345) = 6.649$, $p < 0.001$*** , adj. $R^2 = 0.119$				

Note. B unstandardized regression coefficient*, β* standardized regression coefficient, *CI* confidence interval, *GAF* Global Assessment of Functioning Scale, *HIV* human immune-deficiency virus, *SE* standard error
*p<0.05, **p<0.01, ***p<0.001

Table 3. 4: Linear Regression Analysis of Selected Predictor Variables and WIV-Accuracy Amongst People with Schizophrenia (n = 353)

Predictor Variable	B	95% CI	β	*p*
Age	-0.005	[-0.008, -0.001]	-0.127	0.022*
Sex	0.015	[-0.113, 0.142]	0.013	0.818
Education	0.002	[-0.031, 0.034]	0.005	0.921
HIV Status	0.059	[-0.113, 0.230]	0.036	0.502
Substance Use	0.032	[-0.005, 0.070]	0.096	0.088
Symptom Severity	0.025	[-0.034, 0.084]	0.045	0.410
GAF	0.000	[-0.004, -0.003]	-0.005	0.922
Constant = -0.185 , $F(7,345) = 1.720$, $p = 0.103$, adj. $R^2 = 0.014$				

Note. B unstandardized regression coefficient*, β* standardized regression coefficient, *CI* confidence interval, *GAF* Global Assessment of Functioning Scale, *HIV* human immune-deficiency virus, *SE* standard error
*p<0.05, **p<0.01, ***p<0.001

3.5. Discussion

In this first study of WIV in cognitive performance in SCZ in a LMIC, we provide novel insights into the relationship between WIV and several clinical and demographic variables in this setting. The main findings of this study were 1) increased speed WIV was significantly associated with a diagnosis of SCZ, 2) reduced speed WIV was associated with a higher level of educational attainment and better functional outcomes among people with SCZ, and 3) among people with SCZ, speed and accuracy WIV were significantly associated with age but with opposite directions of effect, and the magnitude of effect was much larger for speed than accuracy.

The finding of a significant relationship between a diagnosis of SCZ and speed WIV in the analysis of the entire sample is in keeping with previous research, which has demonstrated increased WIV in speed measures for cognitive tasks in PSZ (Fassbender et al., 2014; Roalf et al., 2013a; Roalf et al., 2013b). However, in contrast with previous studies, we did not find a significant relationship between accuracy WIV and SCZ (Roalf et al., 2013a; Roalf et al., 2013b). These results may suggest that WIV in speed measures is a more sensitive marker of cognitive dysfunction in SCZ in this and possibly other LMIC settings. In the analysis restricted to people with SCZ, we found an inverse relationship between speed WIV and global functioning. Converging evidence from multiple studies indicates that reduced WIV in reaction time is a predictor of better functional outcomes in SCZ (Rentrop et al., 2010; Vinogradov et al., 1998; Wexler et al., 2004). Although abnormal elevations in WIV have been observed in other neuropsychiatric disorders, measures of speed WIV may be of potential use in clinical practice to identify PSZ at risk of poor functional outcomes and thus, inform treatment decisions. Further, the results of this study support the significance of measures of

speed WIV in our understanding of SCZ. Measures of speed WIV may be used in addition to or as an alternative to mean performance measures in future studies exploring the biological mechanisms contributing to cognitive impairment and functional outcomes in SCZ.

Cognitive function is an important determinant of socio-economic attainment (e.g. occupation and income), and physical and mental health outcomes in the general population as well as in PSZ (Batty et al., 2016; Fioravanti et al., 2012; Kalechstein et al., 2003; Ozawa et al., 2022; Strenze, 2007). Evidence from a recent meta-analysis supports a positive association between educational attainment and cognitive ability (Ritchie & Tucker-Drob, 2018). SCZ is associated with lower educational attainment in both high-income and low- or middle-income countries (Crossley et al., 2022), and therapeutic guidelines recommend interventions to improve educational outcomes in SCZ (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016; National Institute for Health and Care Excellence [NICE], 2014; Norman et al., 2017). This study found that higher educational attainment was associated with lower speed WIV amongst people with SCZ. This finding provides further support for the positive impact of educational attainment on cognitive function, whether measured by WIV or another metric. This observation emphasizes the relevance of interventions to increase educational attainment, and ultimately improve cognitive function, in PSZ in LMICs.

In this study, increased age was significantly associated with both greater accuracy and lower speed WIV amongst people with SCZ. In studies of WIV across the lifespan in the general population, increasing age after early adulthood is associated with a progressive increase in WIV in cognitive performance (Hultsch et al., 2002; MacDonald et al., 2009b; Roalf et al.,

2014a). In this study, the finding of a positive relationship between age and speed WIV provides support for a similar relationship between speed WIV and age amongst people with SCZ. Contrastingly, age had a negative relationship with accuracy WIV. Although this finding was significant, the model predicting accuracy WIV explained a low amount of variance in accuracy WIV, and age had a small regression coefficient. Thus, the finding should be interpreted with caution and requires replication in other studies. However, that age effects are more pronounced on speed than on accuracy measures on cognitive tests has been established in multiple studies, including those using the PennCNB (Gur et al., 2010; Irani et al., 2012; Moore et al., 2019).

There are certain limitations that need to be considered when interpreting the results of the study. There were substantially more males than females in this cohort, which made accurate assessment of the relationship between sex and WIV challenging. The small number of females may have contributed to the null relationship between sex and WIV in this study when previous research has demonstrated sex differences (Roalf et al., 2014a). Future studies should aim at recruiting more female participants. Similarly, the lack of association between HIV status and WIV must be interpreted with caution as the number of HIV positive individuals enrolled in the study was limited. Further, additional clinically relevant variables, such as CD4 count and HIV viral load, should be collected in future studies in order to allow for a more nuanced analysis of the relationship between WIV and HIV. While the inclusion of participants with HIV made it possible to assess the relationship between HIV and WIV in persons with SCZ, this may have affected the assessment of the relationship between WIV and a diagnosis of SCZ. As HIV is associated with cognitive impairment (Keng et al., 2023), future studies aiming to focus on the relationship between WIV and SCZ may consider excluding individuals

with a diagnosis of HIV. Lastly, the assessment of symptom severity in SCZ in this study was limited as it was derived from the SCID and a valid and reliable specific measure, such as the Positive and Negative Syndrome Scale for Schizophrenia (Kay et al., 1987), would be better suited to assess this relationship.

In conclusion, the results of this study extend current knowledge of WIV in cognitive performance in SCZ by exploring its relationship with multiple clinical and demographic variables in a resource-limited setting. Generally, increased speed WIV was associated with SCZ and poorer functioning in the disorder, while no such effects were observed for WIV in accuracy. This finding suggests that WIV for speed measures might be a more sensitive marker of cognitive impairment in PSZ who can still maintain performance accuracy across neuropsychological tasks. The finding of an inverse relationship between educational attainment and speed WIV in this setting provided further evidence for the positive association between education and evening out cognitive function. The significant relationship between speed WIV and SCZ as well as global functioning in the disorder highlight the potential for future research into WIV to extend our understanding of cognitive impairment in SCZ.

Chapter 4: Original Research Article 2

Genome-wide Association Study in 404,302 Individuals Identifies 7 Significant Loci for Reaction Time Variability

Synopsis

In this chapter, the common genetic variants associated with reaction time variability, an index of across-trial WIV, are investigated. Additionally, the functional relevance of the identified risk variants is explored and the genetic overlap of RTV with selected neuropsychological traits is estimated. The work described in this chapter addresses the second aim of the thesis, "*to explore the contributions of common genetic variants to WIV, as measured by reaction time variability*". The chapter is presented as an original research article and has been published in *Molecular Psychiatry.*

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Authorship Statement

I conceptualized the research question and formulated the objectives for this study with input from my doctoral supervisors. I conducted the data analysis under the supervision of AA Shadrin and S Dalvie. I wrote the first draft of the manuscript. All co-authors provided feedback prior to submission to the journal. I submitted the manuscript to the journal and I have responded to the reviewers' feedback with input from all co-authors.

Genome-wide association study in 404,302 individuals identifies 7 significant loci for reaction time variability

Running title**:** GWAS of Reaction Time Variability

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4.1. Abstract

Reaction time variability (RTV), reflecting fluctuations in response time on cognitive tasks, has been proposed as an endophenotype for many neuropsychiatric disorders. There have been no large-scale genome wide association studies (GWAS) of RTV and little is known about its genetic underpinnings. Here, we used data from the UK Biobank to conduct a GWAS of RTV in participants of white British ancestry (*n* = 404,302) as well as a trans-ancestry GWAS meta-analysis (*n* = 44,873) to assess replication. We found 161 genome-wide significant single nucleotide polymorphisms (SNPs) distributed across 7 genomic loci in our discovery GWAS. Functional annotation of the variants implicated genes involved in synaptic function and neural development. The SNP-based heritability (h^2_{SNP}) estimate for RTV was 3%. We investigated genetic correlations between RTV and selected neuropsychological traits using linkage disequilibrium score regression, and found significant correlations with several traits, including a positive correlation with mean reaction time and SCZ. Despite the high genetic correlation between RTV and mean reaction time, we demonstrate distinctions in the genetic underpinnings of these traits. Lastly, we assessed the predictive ability of a polygenic score (PGS) for RTV, calculated using PRSice and PRS-CS, and found that the RTV-PGS significantly predicted RTV in independent cohorts, but that the generalizability to other ancestry groups was poor. These results identify genetic underpinnings of RTV, and support the use of RTV as an endophenotype for neurological and psychiatric disorders.

4.2. Introduction

Elevated intra-individual variability in reaction time, namely increased trial-by-trial fluctuations in response time on cognitive tasks, has been associated with neurodevelopmental and neurodegenerative disorders (MacDonald et al., 2009b). Increased variability in reaction time is thought to reflect disruptions in attentional control and executive function and it has been associated with abnormalities in brain structure and function (Bunce et al., 2013; Fassbender et al., 2014; Haynes et al., 2017b; MacDonald et al., 2009b). Increased RTV has been demonstrated in ADHD, SCZ, bipolar disorder, and major neurocognitive disorders (Brotman et al., 2009; Fassbender et al., 2014; Haynes et al., 2017a; Kaiser et al., 2008; Kofler et al., 2013; Kuntsi & Klein, 2012). The heritability of RTV has been established in twin and family studies ($h^2 = 0.28 – 0.5$)(Crosbie et al., 2013; Kuntsi et al., 2006) and consequently, RTV has been proposed as an endophenotype for some of these disorders.

Measures of RTV and measures of central tendency, such as mean reaction time, are known to be correlated however, it has been suggested that RTV may provide insight into cognitive function over and above mean performance metrics (MacDonald et al., 2009b; Rentrop et al., 2010; Shin et al., 2013). Abnormalities in RTV have been detected in people classified as at risk mental state for psychosis when mean reaction times are normal (Shin et al., 2013). In studies of age-related changes in cognitive performance, RTV has been found to be a better predictor of subsequent cognitive decline than measures of central tendency (Bielak et al., 2010; Lövdén et al., 2007). Additionally, a systematic review of longitudinal changes in RTV found that the association between elevated RTV at baseline and accelerated cognitive decline, mild neurocognitive disorders, dementia, and mortality remained after controlling for mean reaction time (Haynes et al., 2017a). Thus, RTV may offer unique predictive power

beyond the mean and may be useful in detecting early neuropathological changes prior to the onset of more severe cognitive dysfunction. Given the proposed utility of measures of RTV, a better understanding of its neurobiological underpinnings is required.

Despite increasing interest in the biological basis of RTV, its genetic architecture remains poorly understood. A limited number of candidate gene studies have provided evidence for an association of RTV with catecholamine system genes (Cummins et al., 2014; Grant et al., 2014; Krabbendam et al., 2006). However, candidate gene studies have largely failed to identify replicable genes associated with behavioural traits, including RTV, and there has been a shift towards GWAS to identify genotype-phenotype associations using a hypothesis-free approach (Chabris et al., 2012). There has only been one GWAS of RTV to date (n = 857), which identified one genome-wide significant SNP, rs62182100 (Pinar et al., 2018). The significant SNP is an intronic variant located within the *HDAC4* gene, which plays a role in transcriptional regulation and has been implicated in synaptic plasticity, learning and memory (Kim et al., 2012). However, due to the small sample size and the lack of independent replication in this GWAS, insight into the genetic underpinnings of RTV remains limited. A GWAS with a larger sample size may facilitate the identification of more significant loci and provide the power needed for a more comprehensive investigation of the genetic architecture of this trait.

Here, we conduct the largest GWAS of RTV to date with a sample size of 404,302 individuals using data from the UK Biobank. We aim to identify common genetic variants and genes associated with RTV, and we calculate the first h^2_{SNP} estimate for the trait. We also calculate estimates of genetic correlations with neurodevelopmental disorders and other phenotypes that have been previously associated with RTV. Lastly, we test the external validity of our

results by performing polygenic prediction of RTV in independent samples of European and African ancestries.

4.3. Materials and Methods

4.3.1. Participants and phenotype definition

This study used data from the UK Biobank (UKB), obtained under accession number 27412. The UKB is a large-scale biomedical database with genotype and phenotype data for approximately 500,000 individuals (Sudlow et al., 2015). At baseline, a brief cognitive assessment, including a custom-made reaction time test, was administered to participants (aged 40 – 70 years) as part of the fully-automated questionnaire. The UKB reaction time test is based on a Go/NoGo test and is designed to measure processing speed (Fawns-Ritchie & Deary, 2020). Participants were shown 2 cards with symbols on them and asked to push a button as quickly as possible when the symbols on the card matched. The test consisted of 12 trials, 9 of which contained matching cards. The UKB reaction time test has demonstrated good internal consistency (Cronbach $\alpha = 0.85$)(Hagenaars et al., 2016), moderate test-retest reliability (Pearson $r_{12} = 0.55$)(Fawns-Ritchie & Deary, 2020), and good concurrent validity with well-validated tests of reaction time (Fawns-Ritchie & Deary, 2020).

In the discovery and replication GWAS, RTV was operationalized as the intra-individual standard deviation (ISD) of reaction times across correct trials. Prior to calculating the ISD, trials with a reaction time < 50ms (suggesting anticipation instead of reaction), and > 200ms (indicating a response after the cards had disappeared) were excluded. ISD scores were calculated for participants with ≥ 3 correct trials. As RTV was non-normally distributed, RTV values were rank-based inverse normal transformed. Since longer reaction times may result

in an increased ISD for an individual (Stuss et al., 2003), we also calculated the intraindividual coefficient of variation (ICV) for reaction times for all participants. The ICV is calculated by dividing the ISD by the mean reaction time for an individual. For the discovery dataset, we included 405,022 individuals with "white British" ancestry (54% females; mean age 56.88 years), classified according to self-declared ethnicity and genetic principal component analysis. We used all other ancestry groups from the UKB for replication analysis - this included participants who completed the UKB reaction time test with a self-reported ethnicity of "white non-British" (*n* = 28,600), "Asian or Asian British" (*n* = 8,904), or "Black or Black British" (*n* = 7,415), totaling to 44,919 individuals (55% female, mean age 54.27 years) for inclusion in the replication GWAS.

4.3.2. Genome-wide association analysis

GWAS was conducted using version 3 of the UKB genetic data. Genotyping, imputation, and central quality control procedures for the UKB genotypes are described in detail elsewhere (Bycroft et al., 2018). The REGENIE method was used and involves 2 steps. In step 1, polygenic predictors are constructed by fitting a whole genome regression model to the UKB genotype data. Additional quality control filters were applied to the UKB genotype calls using PLINK 2.0 (Chang et al., 2015) prior to conducting step 1 of REGENIE. Quality control steps included removing: 1) individuals with > 10% missing genotype data, 2) SNPs with >10% genotype missingness, 3) SNPs failing the Hard-Weinberg equilibrium tests at $p = 1 \times 10^{-15}$, and 4) SNPs with a minor allele frequency (MAF) < 1% or minor allele count (MAC) < 50. After quality control, 582,052 variants and 405,019 samples were included in step 1 of REGENIE. In step 2 of REGENIE, a linear regression model was used to test for phenotype-genotype associations using imputed UKB genotype data, conditional upon the predictions of the model from step

1. The association model in step 2 included age, sex and the first 10 genetic principal components as covariates. Variants with an INFO score < 0.8 and MAC < 20 were excluded in step 2 leaving 19,963,755 SNPs and 404,302 samples for inclusion in the GWAS.

4.3.3. Replication cohort and meta-analysis

We sought to replicate the lead SNPs from the discovery GWAS in an independent association analysis. First, we used REGENIE to conduct association analysis within all other ancestry groups ("white non-British", ""Asian or Asian British", and "Black or Black British") from the UKB separately. Quality control procedures were identical to those used for the discovery analysis. Following GWAS, the summary statistics for 28,396,731 SNPs (n = 44,873 after quality control) were meta-analysed using an inverse variance based approach implemented in METAL (Willer et al., 2010). To assess for replication, we determined whether lead SNPs from the discovery GWAS reached significance in the replication GWAS (α = 0.05/7; p < 0.0071). Additionally, we examined if the effect directions of the A1 allele of lead SNPs from the discovery GWAS were concordant across the discovery and replication GWAS. A binomial test was performed using R v4.1.0 (R Core Team, 2021) to assess for an excess or deficit of concordant SNPs than would be expected by chance. Lastly, we used METAL to conduct an inverse variance-weighted meta-analysis of the discovery and replication GWAS.

4.3.4. Genomic risk loci characterization

Genomic risk loci for RTV were characterized from the GWAS results using Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) (Watanabe et al., 2017). First, the SNP2GENE function was used to identify independent significant SNPs, defined as SNPs with a p-value $\leq 5 \times 10^{-8}$ and independent of other genome wide significant

SNPs at $r^2 < 0.6$. The correlation estimates were calculated using the 1000 Genomes Project Phase 3 release European reference panel (Abecasis et al., 2010). A genomic risk locus included all SNPs, including those from the reference panel, that were in linkage disequilibrium of $r^2 \geq 0.6$ with an independent significant SNP. Genomic risk loci that were within 250 kilobases (kb) of each other were merged into one locus. Lead SNPs were defined as independent significant SNPs that were independent of each other at $r^2 < 0.1$. Regional visualization plots were produced using LocusZoom (Pruim et al., 2010).

4.3.5. Functional mapping and annotation

The independent significant SNPs and SNPs in LD ($r^2 > 0.6$) with the independent significant SNPs (henceforth referred to as candidate SNPs) were functionally annotated using ANNOVAR(Wang et al., 2010), combined dependent depletion (CADD)(Kircher et al., 2014), RegulomeDB (RDB)(Boyle et al., 2012), and 15-core chromatin states (Ernst & Kellis, 2017). The NHGRI-EBI GWAS catalogue was searched to assess for previous associations of the candidate SNPs. eQTL mapping for significant SNP-gene pairs (FDR $q < 0.05$) was performed using GTEx v8 whole blood and brain tissue (http://www.gtexportal.org/home/datasets), RNAseq data from the CommonMind Consortium (Fromer et al., 2016), and the BRAINEAC database (http://www.braineac.org/).

Identified lead SNPs were mapped to likely target genes using The OpenTargets Variant-to-Gene pipeline which integrates a positional score, based on distance to the canonical transcription start site, with data from quantitative trait loci and chromatin interaction experiments and *in silico* functional predictions (Ghoussaini et al., 2021; Mountjoy et al., 2021). For each lead SNP, we also report the nearest gene identified through positional

mapping using FUMA. Gene-based analysis of 19,129 protein coding genes was performed using MAGMA (de Leeuw et al., 2015) as implemented in FUMA, with a SNP-wise mean model and the 1000 genomes project phase 3 release European reference panel. To control for multiple testing, a Bonferroni corrected *p*-value was used (α = 0.05/19,129 genes tested; $p < 2.61 \times 10^{-6}$). Additionally, gene-set enrichment analysis was conducted using: 1) significant genes from MAGMA gene-based analysis, 2) genes identified through the OpentTargets' Variant-to-Gene pipeline, and 3) genes identified through positional mapping in FUMA. Hypergeometric tests were applied through the GENE2FUNC function in FUMA to assess if the identified genes were over-represented in 15,496 gene sets obtained from MsigDB v7.0 (Liberzon et al., 2015). Bonferroni correction for multiple testing was applied and gene sets with $p < 3.23 \times 10^{-6}$ were considered significant.

4.3.6. Heritability, polygenicity, and discoverability

We used univariate GCTA-GREML analysis (Yang et al., 2011) and MiXeR (Holland et al., 2020) to estimate the proportion of variance explained by common genetic factors, i.e. h^2_{SNP}. The covariates included in the GCTA-GREML analysis were the same as those included in the GWAS. The proportion of causal variants (polygenicity) and the average explained variance per causal variant (discoverability) were estimated using MiXeR v1.2 (Holland et al., 2020). The univariate mixture model considers MAF, sample size, LD structure and genomic inflation to derive estimates of heritability, polygenicity, and discoverability using maximum likelihood estimation.

4.3.7. Genetic correlation and phenotypic associations

Genetic correlations between RTV and phenotypes known to be associated with RTV were calculated using linkage disequilibrium score regression (LDSC)(Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). Summary statistics for general cognitive ability, educational attainment, Alzheimer's disease, post-traumatic stress disorder (PTSD), ADHD, SCZ, neuroticism, intracranial volume, cortical surface area, cortical thickness, and 7 subcortical brain volumes (nucleus accumbens, amygdala, brainstem, caudate nucleus, pallidum, putamen, and thalamus) were used to calculate genetic correlation estimates. **Supplementary Table 4.1 (Appendix 1)** provides further details on the sources of the GWAS summary statistics. Using data from the UKB, the relationships between RTV and the same phenotypes as listed above were assessed using linear regression (**Appendix 1**: **Supplementary Note and Supplementary Table 4.2**).

4.3.8. Comparison with other measures of RTV and mean reaction time

First, we conducted a GWAS of ICV, an alternative measure of RTV, using the UKB reaction time test and the same participants and analysis pipeline as the discovery RTV-GWAS (*n* = 404,302). Next, we assessed the significance and effect direction of lead SNPs from the discovery RTV-GWAS in the ICV-GWAS as well as a publicly available GWAS of mean reaction time in the UKB (Davies et al., 2018). We estimated the genetic correlation between RTV (measured by ISD), mean reaction time, and ICV using LDSC. Lastly, we estimated the genetic correlation between mean reaction time and the same 17 phenotypes from the genetic correlation analyses with RTV (**Appendix 1: Supplementary Table 4.1**). We tested whether the genetic correlations estimates for the 17 traits were different for RTV compared to mean reaction time (**Appendix 1: Supplementary Note**).

4.3.9. Polygenic score validation

For polygenic score validation we used controls from two independent cohorts of European and African ancestry, The TOP Study (Engh et al., 2010) and The SAX Study (Gulsuner et al., 2020), respectively. RTV on a continuous performance test was calculated for 182 healthy controls from the TOP study and 563 controls (people without psychotic disorders) from the SAX study. Additional information on the TOP and SAX study can be found in **Appendix 1: Supplementary Note**. We also assessed the predictive ability of a RTV polygenic score (PGS) for RTV in the "white non-British", "Asian or Asian British", and "Black or Black British" ancestry groups from the UKB.

The RTV-PGS were calculated from Z-score effect size estimates from the discovery RTV-GWAS using a pruning and thresholding approach implemented in PRSice (Choi & O'Reilly, 2019). Prior to PGS calculation, SNPs with MAF < 0.05 were excluded and pruning was performed using an $r^2 < 0.1$ within a 250 kb window. We calculated PGS across 10 *p*-value thresholds (1, 0.1, 0.05, 0.01, 1×10^{-3}, 1×10^{-4}, 1×10^{-5}, 1×10^{-6}, 1×10^{-7}, 5×10^{-8}) in the white non-British participants from the UKB and linear regression models were used to test the association between RTV and PGS at each threshold. The best performing PGS was used to determine the *p*-value threshold for PGS calculation in all other ancestry groups. Sex, age and the first ten principal components were included covariates. For comparison, we calculated a RTV-PGS in each target cohort using PRS-CS (Ge et al., 2019), which uses a Bayesian regression framework and places a continuous shrinkage prior on SNP effect sizes. The 1000 Genomes Phase 3 release European sample (Abecasis et al., 2010) was used as the LD reference panel

for PRS-CS. The Bonferroni correction was applied to account for multiple testing (α = 0.05/19 polygenic scores; $p < 2.63 \times 10^{-3}$).

4.4. Results

4.4.1. Genome-wide associations

Genome-wide association tests for RTV in the discovery analysis identified 161 genome-wide significant SNPs ($p < 5 \times 10^{-8}$) (**Figure 4.1; Appendix 1: Supplementary Table 4.3**). There were 13 independent significant SNPs distributed across 7 genomic loci (**Table 4.1**). Regional visualization plots for the significant loci are depicted in **Figure 4.2** and **Appendix 1: Supplementary Figure 4.3**. Four of the seven genome-wide significant loci have been reported as significant in previous GWAS of general cognitive ability and intelligence (**Appendix 1: Supplementary Table 4.4**). The linkage disequilibrium score regression intercept was 1 (SE = 0.01), consistent with minimal inflation of the test statistic due to population stratification.

None of the lead SNPs from the discovery GWAS reached significance in the replication GWAS (**Table 4.1; Appendix 1: Supplementary Figure 4.1**). Due to the limited number of lead SNPs at a genome-wide significant threshold, binomial tests for concordance were performed using lead SNPs from the discovery GWAS at a suggestive threshold of p of $\leq 5 \times 10^{-5}$. There were 261 lead SNPs at the suggestive level in the discovery GWAS, with 156 of them having concordant direction of effects (binomial test p = 0.047) in the replication GWAS.

Table 4. 1: Genome-wide Significant Loci for the Discovery GWAS of RTV in 404,302 Individuals

					Discovery GWAS					Replication GWAS	
Genomic Risk Locus	Lead Variant	Chr	Position	A1/A2	A1 Freq	Beta	P-value	Top Assigned Gene	Nearest Gene	Beta	P-value
1	rs183204237	2	162188514	C/G	9.79×10^{-4}	-0.21	2.34×10^{-8}	*PSMD14*	*PSMD14*	-0.088	0.46
2	rs35206686	4	152762934	T/TC	0.736	-0.015	6.09×10^{-9}	*FHIP1A*	*RP11-424M21*	-0.004	0.615
3	rs17167210	7	133339343	A/G	0.435	0.013	1.5×10^{-9}	*EXOC4*	*EXOC4*	-0.01	0.141
4	rs35859241	15	51736660	G/A	0.254	-0.014	3.69×10^{-8}	*SCG3*	*RP11-707P17.1*	-0.001	0.864
5	rs912243472	15	74096786	G/GA	0.135	0.018	1.97×10^{-8}	*TBC1D21*	*INSYN1*	0.005	0.575
6	rs1863115	17	44625928	A/C	0.74	0.017	2.47×10^{-10}	*LRRC37A2*	*LRRC37A2*	0.003	0.755
7	rs11697176	20	3831629	T/C	0.112	-0.021	1.9×10^{-8}	*PANK2*	*MAVS*	0.008	0.58

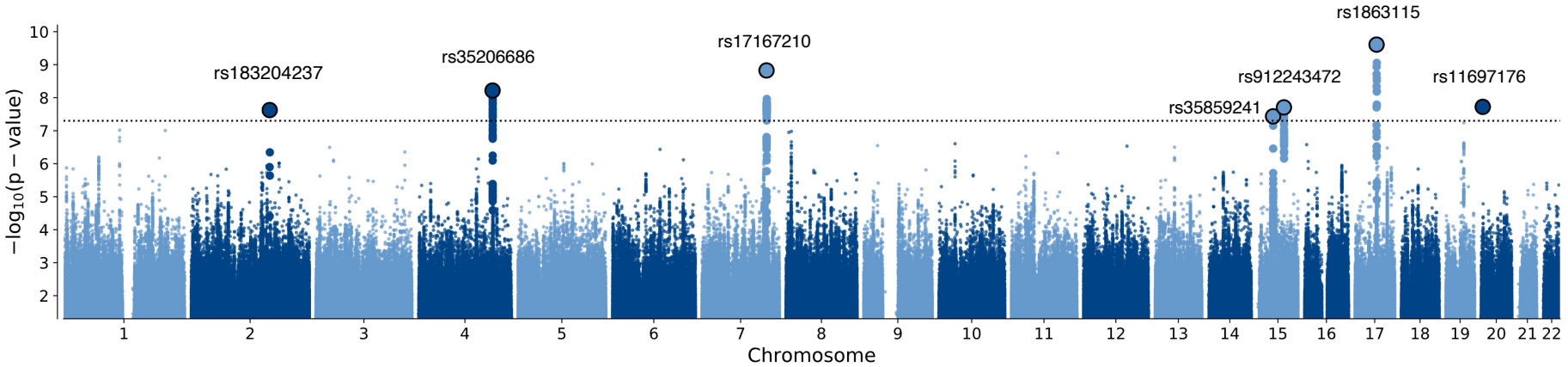

Figure 4. 1: Manhattan Plot of Discovery GWAS for RTV in the UK Biobank

Manhattan plot for the observed -log10 *p*-values for an association with RTV in the discovery GWAS. The dotted line indicates a genome-wide significance threshold of 5 x 10^{-8}. The lead SNPs from the GWAS are outlined in black and the candidate SNPs are shown in bold.

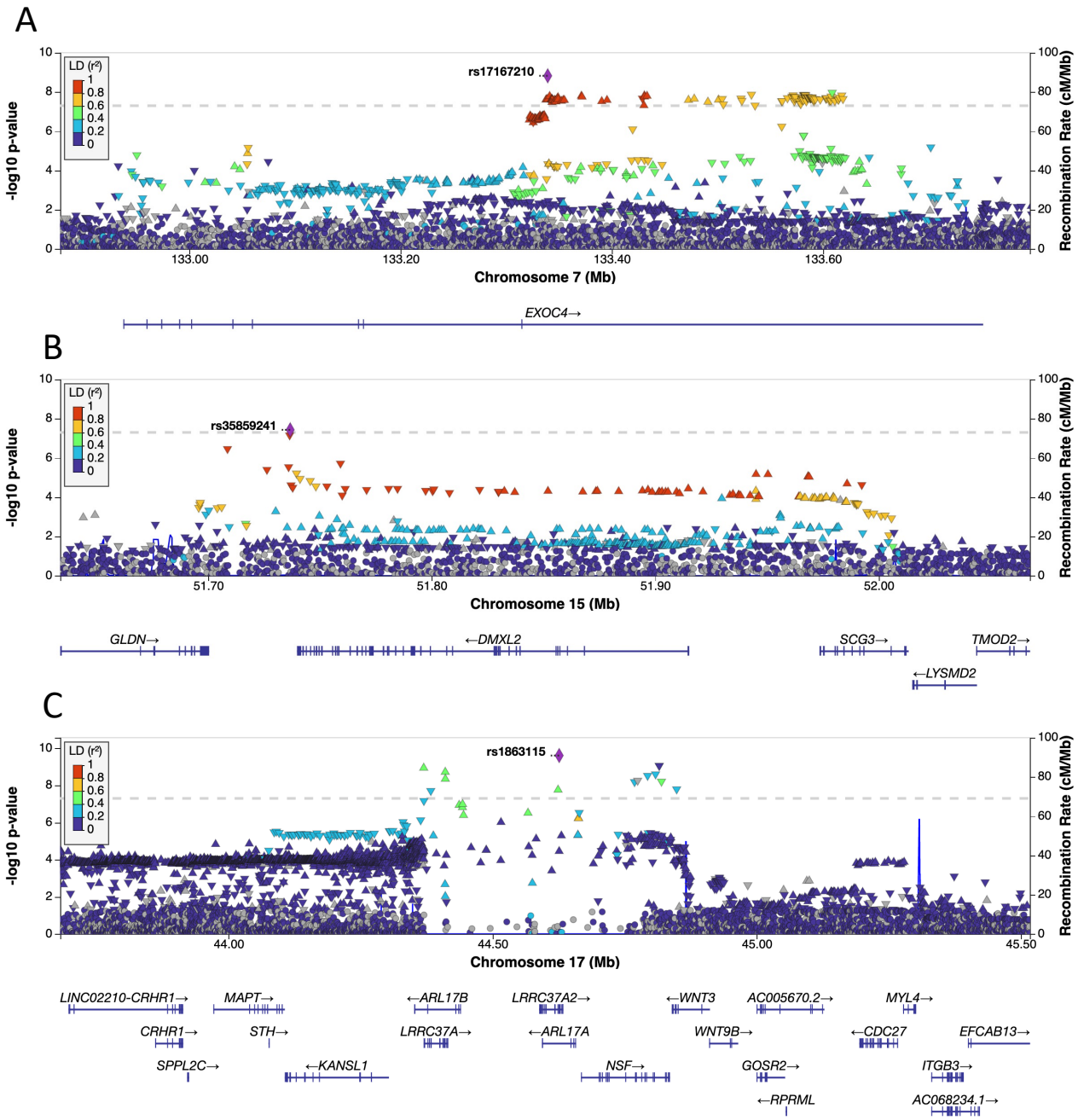

Figure 4. 2: Regional Association Plots for Three Genome-wide Significant Loci in the Discovery RTV-GWAS

Regional plots for rs17167210 **(A)**, rs35859241 **(B)** and rs1863115 **(C)**. The dotted line denotes a genome-wide significance threshold of 5×10^{-8}. SNPs in the genomic risk loci are colour-coded as a function of their linkage disequilibrium r^2 to the lead SNP in the region.

In the meta-analysis of the discovery and replication GWAS (n = 449 175), there were 41 genome-wide significant SNPs ($p < 5 \times 10^{-8}$) distributed across 6 genomic loci (**Appendix 1: Supplementary Figure 4.1 and Supplementary Table 4.5**). Thirty-six of the genome-wide significant SNPs were also significant in the discovery GWAS. Inspection of the quantile-quantile plot for the meta-analysis shows greater test-statistic inflation above the null for moderately significant p-values than in the discovery GWAS (**Appendix 1: Supplementary Figure 4.2**). The linkage disequilibrium score regression intercept for the meta-analysis was 1 (SE = 0.01), suggesting that the inflation of the test statistic reflects true associations with RTV.

4.4.2. Integration with functional genomic data

Each lead SNP from the discovery GWAS was mapped to one gene using the OpenTargets Variant-to-Gene pipeline, resulting in 7 mapped genes (**Table 4.1**). MAGMA gene-based analysis identified 5 genes significantly associated with RTV: *EXOC4* ($p = 6.3 \times 10^{-7}$), *TBC1D21* ($p = 2.57 \times 10^{-6}$), *CNTNAP4* ($p = 2.59 \times 10^{-7}$), *LRRC37A* ($p = 9.81 \times 10^{-10}$), and *NSF* ($p = 4.97 \times 10^{-7}$) (**Appendix 1: Supplementary Table 4.6**). An additional 17 genes were mapped to candidate SNPs from the discovery GWAS using FUMA positional mapping; resulting in a total of 27 input genes (**Appendix 1: Supplementary Table 4.7**) for gene set enrichment analysis. Gene set enrichment analysis did not identify any significant gene sets associated with RTV.

The lead variant for the GWAS, rs1863115 ($p = 2.47 \times 10^{-10}$) (**Figure 4.2, C**), is a non-synonymous exonic variant for *LRRC37A2* and an intronic variant for *ARL17A*. The CADD score for rs1863115 is 18.32, suggestive of variant deleteriousness. Based on annotation by the OpenTargets genetic platform, the most likely gene affected by this variant is *LRRC37A2,* a

gene that encodes an integral component of the cellular membrane. *LRRC37A2* has been associated with intelligence, and mean reaction time in previous GWAS (Davies et al., 2018; Savage et al., 2018)

There was evidence of functionality for variants in genomic risk loci 3 and 4 (**Table 4.1**). The lead variant for locus 3, rs17167210 (p = 1.5 x 10^{-9}), is located in an intron of *EXOC4* and is an eQTL for *EXOC4* and *LRGUK* in brain tissue (CommonMind Consortium) (**Figure 4.2, A**). A nearby intronic variant, rs11768150 (R^2 = 0.88, p = 1.71 x 10^{-7}), has a CADD score of 13.5, suggestive of variant deleterious, and a RegulomeDB score of 3a, indicating that the variant is likely to be involved in gene regulation. The lead variant for locus 4, rs35859241 (p = 3.69 x 10^{-8}), is an eQTL for *SCG3* and *GLDN* in brain tissue (CommonMind Consortium, GTEx Brain). This variant is in LD with rs2606134 (R^2 = 0.81, p = 1.14 x 10^{-4}), which is located within the 5' untranslated region of *SCG3* (**Figure 4.2, B**). The SNP, rs2606134, has a CADD score of 13.15 and a RegulomeDB score of 2b, suggesting that this variant may be biologically relevant.

4.4.3. Estimating heritability, polygenicity, and discoverability

The h^2_{SNP} for RTV was estimated at 0.029 (SE = 0.002) using GCTA-GREML. MiXeR analysis suggested that RTV is highly polygenic with an estimated 6,800 causal variants explaining the h^2_{SNP} for RTV. As expected for a trait with a low h^2_{SNP} and high polygenicity, discoverability was low ($\sigma_2\beta$ = 5.38 x 10^{-6}, SD = 2.85 x 10^{-7}) indicating that most SNP-associations have a weak effect. Akaike's Information Criteria (AIC) for MiXeR analysis was 18.39 indicating reliable model fit.

4.4.4. Genetic correlations and phenotypic associations

We assessed the genetic correlations and phenotypic relationships between RTV and 17 traits that have been posited to be associated with RTV using LDSC and linear regression respectively (**Figure 4.3; Appendix 1: Supplementary Tables 4.8 and 4.9**). After Bonferroni correction, we found significant genetic correlations (α = 0.05/19 traits; $p < 2.63 \times 10^{-3}$) between RTV and general cognitive ability (r_g = -0.44, SE = 0.03), educational attainment (r_g = -0.23, SE = 0.03), SCZ (r_g = 0.26, SE = 0.03), and neuroticism (r_g = 0.13, SE = 0.03). The analysis of phenotypic data from the UKB revealed a significant relationship between RTV and several traits, including those that showed significant genetic correlations with RTV (**Figure 4.3, Appendix 1: Supplementary Table 4.9**).

4.4.5. Comparison with other measures of RTV and mean reaction time

We sought replication of the 7 lead SNPs from the discovery RTV-GWAS in the GWAS of ICV and found that all lead SNPs were significant (α = 0.05/7; $p < 0.0071$) in the ICV-GWAS (**Appendix 1: Supplementary Table 4.10**). Similar to the replication analyses described earlier, we used the 261 lead SNPs from the discovery GWAS at a suggestive threshold of $p \leq 5 \times 10^{-5}$ to conduct binomial tests for concordance. All lead SNPs from the discovery RTV-GWAS had a concordant direction of effect in the ICV-GWAS. We found significant genetic correlations between RTV and ICV (r_g = 0.89, SE = 0.01) as well as RTV and mean reaction time (r_g = 0.69, SE = 0.02). Consistent with the relatively high genetic correlation between RTV and mean RT, the number of lead SNPs from the RTV-GWAS that showed a concordant direction of effect in the mean reaction time GWAS was greater than expected by chance (binomial test $p < 2.2 \times 10^{-16}$). However, only one of the lead SNPs from the discovery RTV-GWAS reached significance ($p < 0.0071$) in the GWAS of mean reaction time. Further, we found that 7

(*ARL17A, ARL17B, LRRC37A2, NSF, WNT3, TBC1D21, CDC27)* of the 27 genes identified in the RTV-GWAS had a documented association with mean reaction time in the GWAS catalogue (Sollis et al., 2023).

Lastly, we found that the genetic correlations between RTV and 17 selected traits and mean reaction time and the same 17 traits were similar for most traits. Notably, we found significant differences in the genetic correlations between RTV and educational attainment, general cognitive ability, and ADHD when compared to the genetic correlations between mean reaction time and the same traits (**Appendix 1: Supplementary Table 4.8**). We show that ADHD has a nominally significant positive genetic correlation with RTV (r_g = 0.1, SE = 0.02, p = 5.1 x 10^{-3}) and a nominally significant negative correlation with mean reaction time (r_g = -0.06, SE = 0.03, p = 0.03) (**Figure 4.3; Appendix 1: Supplementary Figure 4.4 and Supplementary Table 4.8**). The magnitude of genetic correlations was significantly greater for RTV compared to mean rection time for educational attainment and general cognitive ability (**Appendix 1: Supplementary Figure 4.4 and Supplementary Table 4.8**).

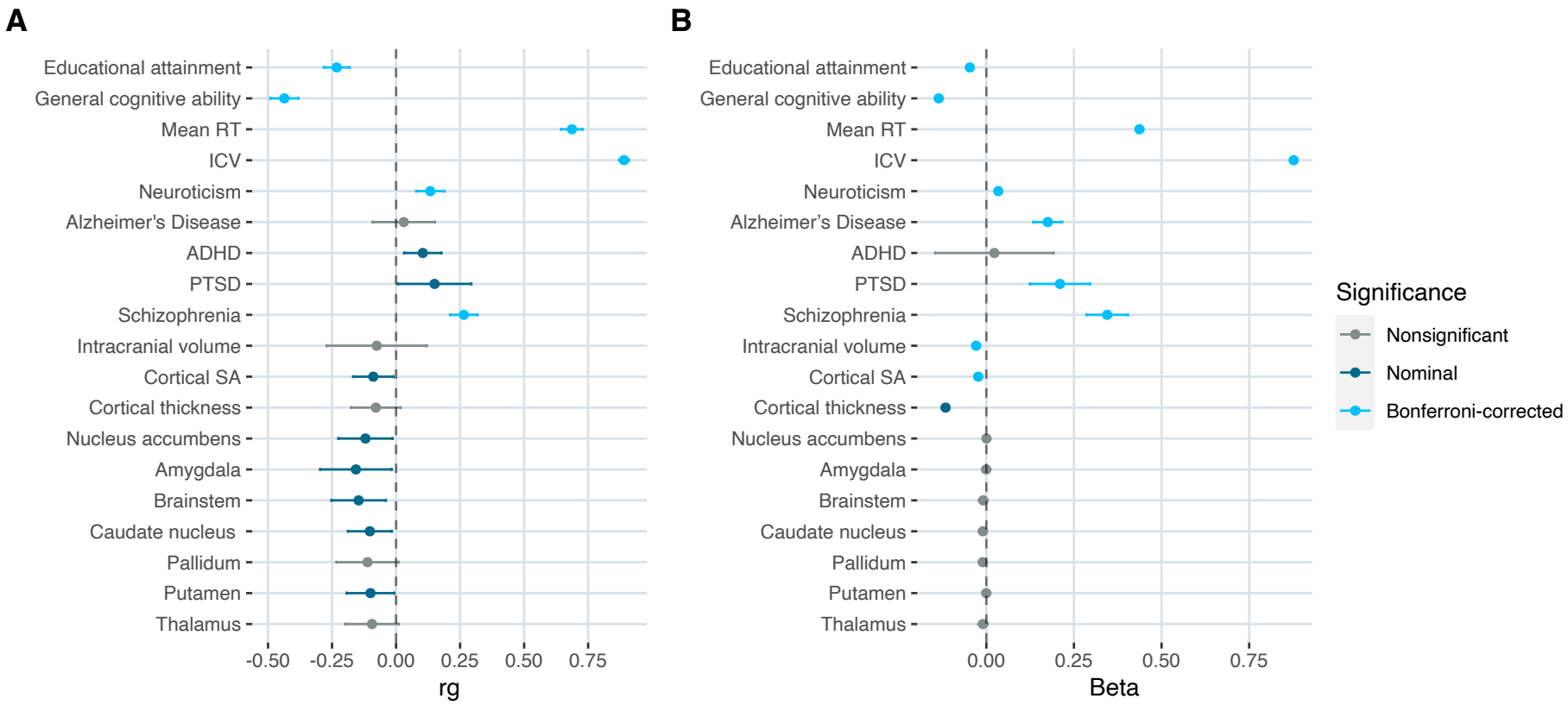

Figure 4. 3: Genetic Correlations and Phenotypic Associations Between RTV and 19 Selected Traits.

Genetic correlations were calculated with LD score regression using SNP summary statistics from discovery RTV-GWAS and publicly available summary statistics for other traits (**Appendix 1: Supplementary Table 4.1**). Associations between RTV and the same 19 traits were calculated using phenotypic data from the UK Biobank (**Appendix 1: Supplementary Methods)**. Point estimates for correlations and beta coefficients are shown with 95% confidence intervals. Dark blue dots indicate nominally significant *p*-values and light blue dots indicate significant *p*-values after Bonferroni correction.

4.4.6. Polygenic prediction of RTV

To evaluate the replicability and predictive ability of the results from our discovery GWAS, we calculated a PGS for RTV in the five independent target samples using PRSice and PRS-CS. For the PGS calculated using PRSice, the most significant association between the RTV-PGS and RTV in non-British European participants from the UKB was achieved when all SNPs surviving LD pruning (n = 166 662) were included in the PGS calculation (p-value threshold = 1) (**Appendix 1: Supplementary Table 4.11**). The variance explained by this PGS was r^2 = 0.0027 (p = 6.09 x 10^{-18}). The PRSice RTV-PGS performed poorly in the other ancestry groups from the UKB and there were no significant associations between the PGS and RTV in the South Asian or African ancestry groups (**Figure 4.4**). There was an improvement in predictive power when using PRS-CS to calculate the PGS and there was a significant association between the RTV-PGS and RTV in the non-British European (r^2 = 0.0048, p = 3.08 x 10^{-31}) and South Asian ancestry groups (r^2 = 0.0012, p =1.73 x 10^{-3}) from the UKB (**Figure 4.4**). The PRSice and PRS-CS RTV-PGS did not predict RTV in controls from the TOP and SAX study (**Appendix 1: Supplementary Table 4.11 and Supplementary Figure 4.5**).

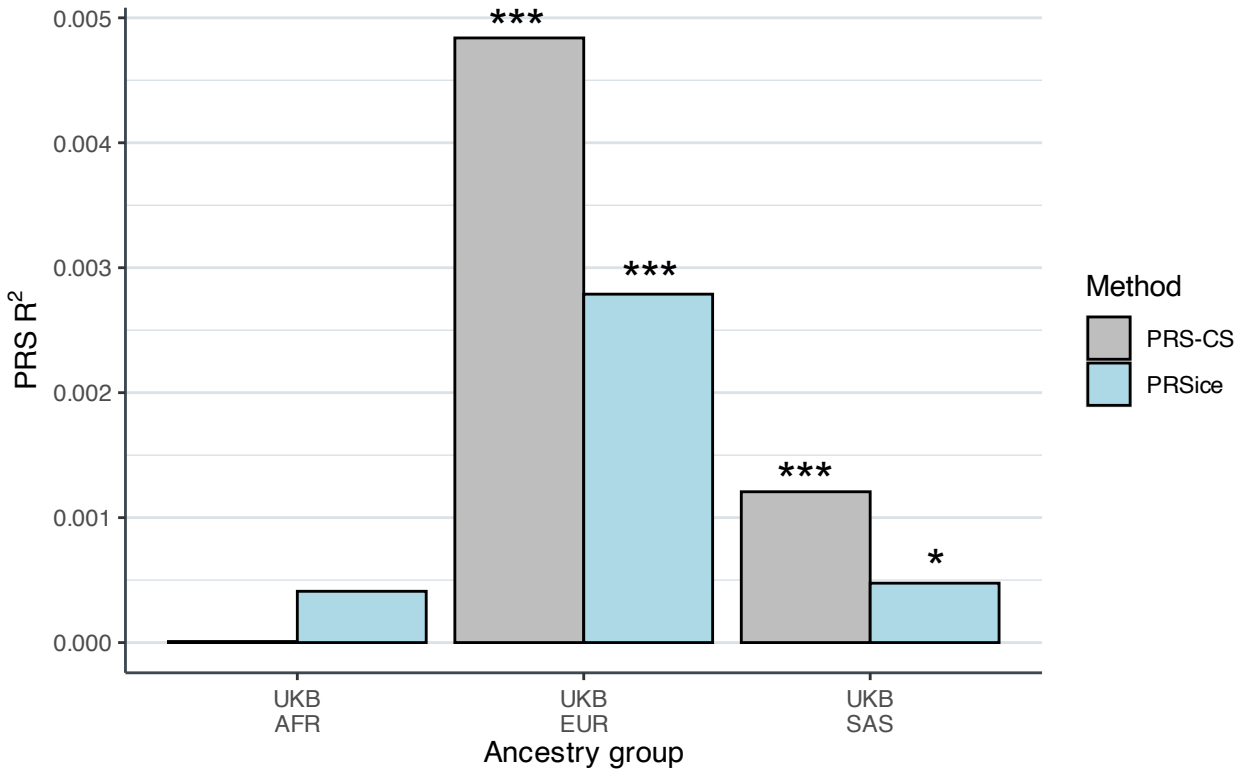

Figure 4. 4: Bar Chart Showing the Predictive Accuracy of the RTV-PGS in Three Independent Cohorts

Prediction of RTV by polygenic score (PGS) in the African, non-British European, and South Asian ancestry groups from the UK Biobank. The predictive accuracy of the PGS (R^2) was assessed in each cohort for a PGS calculated using two methodologies, PRSice and PRS-CS. PRSice PGS were calculated using all single nucleotide polymorphisms surviving LD pruning from the discovery GWAS (*p*-value threshold of 1).

*p<0.05, ***p<2.63 x 10^{-3}

4.5. Discussion

Using UKB data, we have performed the largest GWAS of RTV to date and have made several contributions to our understanding of the genetic basis of this cognitive trait. We identified 161 genome-wide significant SNPs for RTV distributed across 7 genomic loci. We identified several genes that may play a role in RTV, many of which have been associated with cognitive traits previously. We provide the first h^2_{SNP} estimate for RTV, and the first estimates for genetic correlations between RTV and several neuropsychiatric traits. We demonstrate that RTV-PGS derived from the discovery GWAS can significantly predict RTV in an independent cohort, but that the predictive ability declines if the discovery and target populations are of different ancestries.

The genes identified by the GWAS may provide insight into the biological underpinnings of RTV. Although the exact role that many of the identified genes may play in RTV is unclear, several are worthy of further investigation. For example, two of the significant genes, contactin associated protein family member 4 (*CNTNAP4)* and N-ethylmaleimide sensitive factor, vesicle fusing ATPase (*NSF*) encode proteins that play a role in synaptic function. *CNTNAP4* is involved in the synaptic transmission of dopamine and GABA (Karayannis et al., 2014) and *NSF* regulates glutamate receptor binding activity.(Hanley, 2007; Nishimune et al., 1998) Alterations in dopaminergic, glutaminergic and GABAergic activity have been associated with RTV (MacDonald et al., 2009a; MacDonald et al., 2009b; Pouget et al., 2009; Russell et al., 2006) and thus, further exploration of the association between RTV and *CNTNAP4* and *NSF* may be warranted. Variants in *EXOC4* and *SCG3* showed evidence of regulatory functionality and variant deleteriousness. Both genes are highly expressed in the brain and have been associated with cognitive traits in previous GWAS (Lam et al., 2017;

Savage et al., 2018). *EXOC4* encodes a component of the exocyst complex which plays a role in multiple physiological processes, including neuronal development (Martin-Urdiroz et al., 2016; Mei & Guo, 2018). *SCG3* encodes a member of the granin family of neuroendocrine secretory proteins and is involved in secretory granule biosynthesis and the storage and transport of neurotransmitters (Hosaka & Watanabe, 2010; Taupenot et al., 2003). Another identified gene, inhibitory synaptic factor 1 (*INSYN1),* is involved in post-synaptic inhibition in the central nervous system (Uezu et al., 2016) and may be considered for further study. *INSYN1* is a novel association for a cognitive trait but it has been associated with psychiatric disorders, including ADHD (Karlsson Linnér et al., 2021), PTSD (Wendt et al., 2022), and Tourette syndrome (Yu et al., 2019). Many of the identified genes play a role in neural development and synaptic functioning, suggesting an important role for these processes in the biology of RTV.

We reported an h^2_{SNP} of 3%, high polygenicity, and low discoverability for RTV. It is possible that the high polygenicity, despite the relatively low heritability, may be explained by the range of exogenous factors, such as age, sex, handedness, visual acuity, and treatment effects that influence RTV (Finkel & McGue, 2007; Kofler et al., 2013; Woods et al., 2015). We hypothesize that a large proportion of the identified 6,800 causal variants may be associated with these exogenous factors and thus, only have indirect and weak effects on RTV.

We found that a PGS, derived from the RTV-GWAS in white British participants from the UKB, was significantly predictive of RTV in the UKB white non-British participants, explaining 0.5% of the variance in the measure, which is expected with a h^2_{SNP} of 3% (Choi et al., 2020). The predictive accuracy of the PGS was substantially lower in non-European ancestry populations.

This is in keeping with prior work on the generalizability of PGS across ancestrally diverse populations with the predictive accuracy of the PGS decreasing as the genetic distance between the discovery and target populations increases (Majara et al., 2023). These results further emphasize the need to increase the representation of ancestrally diverse populations in genomic studies.

We found significant positive genetic correlations between RTV and SCZ, and neuroticism. The result for SCZ is consistent with previous findings of increased RTV in people with SCZ (Fassbender et al., 2014; Kaiser et al., 2008). It is hypothesized that the elevations in RTV reflect cognitive control deficits that occur in the disorder (Fassbender et al., 2014). The positive genetic correlation between RTV and neuroticism is supported by our phenotype analysis, which demonstrate a positive relationship between the two phenotypes. To our knowledge, the association between these two traits has not been studied and future research is needed to explore the mechanisms that contribute to a relationship between RTV and neuroticism. There were significant negative genetic correlations between educational attainment, and general cognitive ability. This result is in keeping with the negative relationship between these two traits and RTV on the phenotypic level reported in previous literature (Der & Deary, 2018; Rabbitt et al., 2001).

As our primary measure of RTV (ISD) is often highly correlated with mean reaction time (Stuss et al., 2003), we conducted an additional GWAS of another measure of RTV, the ICV. ICV is the ratio of a participant's ISD to their mean reaction time and provides a certain degree of control for mean reaction time. We found the genetic basis of both measures of RTV, ISD and ICV, to be similar. All lead SNPs from the discovery RTV-GWAS reached significance in the ICV-

GWAS and showed a consistent direction of effect. The significant high genetic correlation between ISD and ICV provides additional support for consistency between the common genetic determinants of both measures of RTV. Consistent with the strong phenotypic association between RTV and mean reaction time, we found evidence of similarities in the common genetic determinants of the two traits. However, we also demonstrate differences in the genetic basis of RTV and mean reaction time and show that most of the lead SNPs and identified genes from the RTV-GWAS are not associated with mean reaction time. Additionally, the results from our genetic correlation analyses show that while the patterns of correlation with the 17 selected phenotypes are similar for RTV and mean reaction time, there are significant differences in the magnitude and direction of correlation for certain phenotypes (e.g. educational attainment, general cognitive ability and ADHD. These analyses demonstrate distinctions in the common genetic variants associated with RTV and mean reaction time and provide support for our approach of studying RTV separately to mean reaction time.

There are some limitations to this study. First, the UKB reaction time test is brief and consists of fewer trials than are typically used in simple reaction time tests. This paucity of trials may have reduced the reliability of the measurement thereby affecting our ability to accurately capture RTV for participants, contributing towards the low estimate for h^2_{SNP}. While the associations between RTV and other mental health and cognitive phenotypes in the UKB are in keeping with the associations observed in previous studies of RTV using validated reaction time tests, future studies should consider using a more comprehensive assessment of reaction time. Second, the assessment of RTV differed between the UKB, SAX, and TOP study and heterogeneity in the phenotype may have affected comparisons of RTV among studies.

Third, there is a lack of well-powered studies with which to conduct a replication GWAS. The moderate sample size of the replication study and limitations pertaining to the trans-ancestry replicability of risk variants may account for the non-replication of the lead SNPs from our discovery GWAS. Fourth, the low h^2_{SNP} of RTV may have affected the accuracy and predictive power of the RTV-PGS. While this low h^2_{SNP} limits the potential use of the PGS to predict RTV, we were still able to fulfil the aim of the PGS analyses, which was to evaluate the replicability of the results from the discovery GWAS. Lastly, we used self-reported ethnicity as a population descriptor for participants from the UKB. While using the ethnic groups provided by the UKB facilitates comparability with other studies using the same data, future work should consider alternative population descriptors that are better able to capture genetic variation between groups.

4.6. Conclusion

In summary, we have conducted the first large-scale GWAS of RTV using 404,302 samples and identified 7 independent associated loci. Several of the implicated genes are involved in neural development and synaptic function and are known to be associated with other cognitive traits. These findings suggest that disruptions to these processes may affect shared biological mechanisms responsible for maintaining the integrity of various aspects of cognitive function. Despite the relatively low h^2_{SNP} of RTV observed in our study, it provides evidence that there is a genetic contribution to the trait. Future studies may leverage these findings to improve our understanding of the genetic mechanisms contributing to RTV and gain novel insight into the biological underpinnings of related complex disorders, like SCZ.

This manuscript was published with Supplementary Tables and a Supplementary Note which may be found in Appendix 1 of this thesis.

Chapter 5: Original Research Study 3

Exploring the Genetic Basis of Cognitive Dysfunction in Schizophrenia: Insights from Genomic Structural Equation Modelling

Synopsis

In this chapter, the genetic overlap between genetically determined cognitive factors, corresponding to broad cognitive abilities, and schizophrenia is investigated. Three latent cognitive factors are derived by applying Genomic Structural Equation Modelling to 12 cognitive traits measured in the UK Biobank. The shared genetic determinants of the latent cognitive factors, schizophrenia, and schizophrenia symptom dimensions are investigated using a variety of statistical approaches and data from the largest PGC-Schizophrenia GWAS and The TOP Study. The work described in this chapter addresses the third aim of the thesis, "*to investigate the overlap in the common genetic underpinnings of cognitive function and schizophrenia*".

Contribution of Collaborators

I conceptualized the research question and formulated the objectives for this study with input from my doctoral supervisors. I conducted the data analysis under the supervision of AA Shadrin and S Dalvie. I wrote this chapter with feedback from my supervisory team as well as the following collaborator(s):

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5.1. Abstract

Cognitive impairment is a major determinant of functional outcomes in schizophrenia and efforts to understand the biological basis of cognitive dysfunction in the disorder are ongoing. Previous studies have suggested genetic overlap between global cognitive ability and schizophrenia, but further work is needed to delineate the shared genetic architecture. In this chapter, Genomic Structural Equation Modelling is applied to 12 cognitive traits measured in the UKB identify to identify latent cognitive factors capturing broad genetic liabilities. The overlap between the latent cognitive factors, schizophrenia, and schizophrenia symptom dimensions is explored using a complementary set of statistical approaches applied to data from the latest PGC-SCZ GWAS (Ncase = 53,386, Ncontrol = 77,258) and The TOP Study (Ncase = 306, Ncontrol = 1060). A three-factor model, with visuo-spatial, verbal analytic and decision/reaction time factors, was found to best explain the genetic correlations between the UKB cognitive tests. Global genetic correlations showed a significant but moderate negative genetic correlation between each cognitive factor and schizophrenia. Local genetic correlations were largely consistent with these findings and implicated unique genomic regions for each cognitive factor. There was evidence of substantial polygenic overlap between each cognitive factor and schizophrenia but it was found that most loci shared between the latent cognitive factors and schizophrenia have unique patterns of association with the cognitive factors. Biological annotation of the shared loci implicated gene-sets related to neurodevelopment and neuronal function. Lastly, the results show that the common genetic determinants of the latent cognitive factors are distinct from those associated with schizophrenia symptom dimensions. Overall, these findings inform our understanding of cognitive function in schizophrenia by demonstrating important differences in the shared genetic architecture of schizophrenia and broad cognitive abilities.

5.2. Introduction

As discussed in Chapter 1, a global deficit in cognitive function is characteristic of SCZ with evidence indicating greater impairment for specific cognitive domains such as executive function, attention, episodic memory, and motor speed, compared to others (Fioravanti et al., 2012; Gebreegziabhere et al., 2022; Gur et al., 2015; Tschentscher et al., 2023). Cognitive impairment is a major determinant of functional outcomes in SCZ yet most existing therapies for SCZ do not address cognitive symptoms (Kharawala et al., 2022; McCutcheon et al., 2023). Thus, there has been increasing interest in identifying the biological basis of cognitive dysfunction in SCZ in order to facilitate the identification of novel therapeutic targets (McCutcheon et al., 2023).

Despite the high heritability of both SCZ and cognitive ability, insights into the genetic influences of cognitive impairment in SCZ remain limited. Molecular genetic studies have identified rare and common genetic variants that are associated with both SCZ and cognitive function, implicating genes involved in neurodevelopment, synaptic integrity, and neurotransmission (Murillo-García et al., 2022; Smeland et al., 2020a). As demonstrated in Chapter 4 of this thesis, there is a significant positive genetic correlation between SCZ and RTV, a marker of cognitive dysfunction, and the genes implicated in RTV share biological functions with genes associated with SCZ. However, findings from studies investigating the association between genetic liability for SCZ and cognitive impairment in individuals with SCZ have been inconsistent. Some studies have found that a PRS for SCZ is negatively associated with cognitive ability (Legge et al., 2021; Nakahara et al., 2018) while others have found no association (Engen et al., 2020; Richards et al., 2020; Xavier et al., 2018).

One possible explanation for the inconsistent results is that previous studies have typically focused on the association between the genetic determinants of SCZ and a single measure of general cognitive ability, such as the *g* factor. Given that performance across cognitive domains is known to be differentially affected by SCZ, the use of a broad measure of cognitive ability may prevent a more detailed examination of the genetic contributions to cognitive impairment in the disorder.

Additionally, SCZ is characterized by clinical and biological heterogeneity, and most efforts to identify biomarkers for cognitive impairment in the disorder do not adequately consider this variability. Heterogeneity in schizophrenia may be understood in three ways: 1) clinical heterogeneity, which refers to diverse symptom profiles classified under the same disorder; 2) biological heterogeneity, which encompasses different biological mechanisms that underpin the same symptoms; and 3) environmental heterogeneity, which includes different environmental factors that either predispose individuals to or protect them from the same symptoms (Wolfers et al., 2018). There is evidence to suggest that unique biological processes contribute to the various symptom dimensions in SCZ (McCutcheon et al., 2020; Owen et al., 2016; Xavier & Vorderstrasse, 2017) and thus, it is plausible that the degree of genetic overlap with cognitive function will differ across the SCZ symptom dimensions. However, few genetic studies have taken a dimensional approach to assessing this relationship and thus, may be missing unique patterns of overlap between schizophrenia symptom dimensions and cognitive impairment. An improved understanding of the shared biology across schizophrenia symptom dimensions and domains of cognitive impairments may facilitate the identification of subgroups within the disorder characterised by shared biology.

This chapter describes a nuanced approach to the investigation of the shared genetic determinants between cognitive function and SCZ. Genomic Structural Equation Modelling (Genomic SEM) is applied to 12 cognitive measures from the UKB to derive latent factors corresponding to broad dimensions of cognitive function. A range of statistical approaches is used to identify genetic variants shared between the broad dimensions of cognitive function and SCZ. Lastly, this chapter explores whether the phenotypic distinction between cognitive dysfunction and other schizophrenia dimensions may be explained by differences in the underlying genetic architecture.

5.3. Materials and Methods

5.3.1. Sample description

This study used data from the UKB, a large-scale biomedical database with genotype and phenotype data for approximately 500,000 people (Sudlow et al., 2015). The UKB has ethical approval (REC reference number – 11/NW/0382) and is overseen by an Independent Ethics and Governance council. Data for this study was obtained under accession number 27412. The analysis uses genotype and cognitive data for individuals with a self-reported ethnicity of "white British" or "white non-British". Cognitive tests included in this study were completed during the baseline assessment, and later assessments that formed part of the UKB imaging study. Sample sizes for each cognitive trait vary (n = 28,156 – 436,853; **Figure 5.1**) and participants' ages range from 40-70 years at baseline and 45-75 years at later assessments.

5.3.2. Definition of cognitive phenotypes

This study included 12 cognitive measures that were derived from cognitive tests administered as part of the baseline and follow up assessments for the UKB. The four cognitive tests that were administered at baseline are Fluid Intelligence, Reaction Time, Numeric Memory, and Pairs Matching Test. The six tests that were administered during a follow up assessment are Prospective Memory, Matrix Pattern Completion, Paired Associate Learning (PAL), UKB Symbol Digit Substitution, Tower Rearranging, UKB Trail Making Test – Part A and B (TMT-A and TMT-B). All cognitive tests were fully automated and were designed to be administered with minimal supervision. A detailed description of each cognitive test is provided in **Appendix 2**.

5.3.3. Genome-wide association analyses

Version 3 of the UKB genetic data was used for this study. Genotyping, imputation, and central quality control procedures for the UKB genotypes are described in detail elsewhere (Bycroft et al., 2018). Univariate GWAS for each cognitive phenotype was conducted using the REGENIE tool (Mbatchou et al., 2021), which consists of two steps. For step 1, polygenic predictors are calculated by fitting a whole genome regression model to genotype data. Prior to conducting step 1, the following quality control filters were applied to the UKB genotype calls: removal of individuals with > 10% missing genotype data, removal of SNPs with > 10% genotype missingness, removal of SNPs failing the Hardy-Weinberg equilibrium tests at $p = 1 \times 10^{-15}$, and removal of SNPs with a MAF < 1%. After quality control, 581,299 variants remained for inclusion in step 1 of the analysis. For step 2, a linear regression model is used to test for phenotype-genotype associations using imputed genotype data, conditional upon the predictions of the model from step 1. Variants with an INFO score < 0.8 and MAC < 20 were excluded from this step, leaving a maximum of 20,241,796 variants for analysis. Sex, age, age^2, age by sex interaction, assessment centre, genotype array, and the first 40 genetic principal components were included as covariates in each GWAS.

5.3.4. Estimations of SNP-based heritability and genetic correlations

The h^2_{SNP} for each cognitive phenotype from the UKB was estimated using LDSC (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). LDSC was also used to estimate the genetic correlations between the 12 cognitive phenotypes.

5.3.5. Genomic structural equation modelling

Exploratory and confirmatory factor analysis of the 12 UKB cognitive phenotypes was conducted. First, the multivariable extension of LDSC employed in Genomic SEM was used to

derive a genetic covariance matrix (S) and sampling covariance matrix (V). Next, exploratory factor analysis (EFA) with promax rotation was conducted on the standardized S matrix using the R package, *stats* (R Core Team, 2022). Results from the EFA were used to guide confirmatory factor analysis (CFA) for a one, two-, and three-factor model. CFA was performed using Genomic SEM and standardized factor loadings of > 0.4 were retained for CFA. Model fit for each factor model was assessed using recommended fit indices: standardized root mean square residual (SRMR), model $\chi 2$ statistic, Akaike Information Criterion (AIC), and Comparative Fit Index (CFI). Model fit was considered acceptable for CFI values ≥ 0.90 and SRMR values ≤ 0.10 (Grotzinger et al., 2019). A three-factor solution demonstrated superior model fit to a one- or two-factor solution and was selected for subsequent analysis.

5.3.6. Multivariate GWAS in Genomic SEM

Following identification of the confirmatory factor model that best explained the genetic covariance structure among the UKB cognitive phenotypes, Genomic SEM was used to estimate the individual SNP associations with each latent factor in the model. As the cross-trait intercepts estimated by multivariable LDSC account for sample overlap, SNP association estimates derived using Genomic SEM are robust to varying and unknown degrees of sample overlap across the contributing univariate GWAS (Grotzinger et al., 2019). The multivariate GWAS was conducted using summary statistics for the univariate GWAS for each cognitive phenotype. Prior to conducting the multivariate GWAS, effect alleles were aligned across univariate GWAS and beta coefficients were standardized. Summary statistics for input into the multivariate GWAS were restricted to SNPs that were present for all 12 cognitive phenotypes and present in the 1000 Genomes Project Phase 3 release European reference

panel (Abecasis et al., 2010). After filtering, 8,041,728 SNPs remained for inclusion in the multivariate GWAS. The effective sample size for each latent factor was calculated using methodology described in a previous publication (Mallard et al., 2022).

5.3.7. Estimation of genetic overlap between cognitive factors and schizophrenia

The genetic overlap between the three latent cognitive factors and SCZ was explored using summary statistics from the multivariate GWASs and for participants of European ancestry in the latest PGC-SCZ GWAS (Ncase = 53,386, Ncontrol = 77,258) (Trubetskoy et al., 2022).

First, global genetic correlations between the latent cognitive factors and SCZ were estimated using LDSC (Frei et al., 2019). Bivariate MiXeR was also used to estimate the number of phenotype-specific and shared causal variants between each cognitive factor and SCZ. A bivariate Gaussian mixture model with four components was constructed using summary statistics for each cognitive factor and SCZ. The four components of the model represent 1) SNPs with a null effect for both phenotypes, 2 and 3) SNPs with a non-null effect for either the first or second phenotype, and 4) SNPs with a non-null effect for both phenotypes. Model fit was evaluated by the AIC.

Next, local genetic correlations between the latent cognitive factors and SCZ were estimated using Local Analysis of [co]Variant Association (LAVA) (Werme et al., 2022). For each phenotype, LAVA was used to estimate the genetic variance across 2,495 semi-independent genetic loci of approximately equal size (~1 Mb) defined by Werme et al. (2022). Loci with a significant local SNP based heritability (α = 0.05/2,495 loci; $p < 2 \times 10^{-5}$) for each phenotype were included in the bivariate analysis. LAVA estimates local genetic correlations for each

phenotype pair by constructing a matrix of local genetic covariance for each locus using the method of moments.

Lastly, conjFDR analysis (Andreassen et al., 2013b; Smeland et al., 2020b) was conducted to identify individual SNPs that were jointly associated with each latent cognitive factor-SCZ pair. The conjFDR method is an extension of the conditional false discovery rate approach (condFDR) (Andreassen et al., 2013a; Andreassen et al., 2013b). For each latent cognitive factor-SCZ pair, the SNP associations with the latent cognitive factor are used to re-rank the test statistics and recalculate the significance of the SNP associations with SCZ. The phenotypes are then reversed and the strength of a SNP association with each cognitive factor conditional on the SNP association with SCZ is re-calculated. Next, conjFDR analysis was used to estimate the likelihood, represented as a conjFDR value, that a SNP has a non-null association with both phenotypes in a phenotype pair. A conjFDR value < 0.05 was considered significant.

5.3.8. Functional annotation

I used standard Functional Mapping and Annotation of Genome-wide Association Studies (FUMA) definitions to define genomic loci, lead SNPs, independent significant SNPs, and candidate SNPs by clumping the conjFDR output for each latent cognitive factor-SCZ pair at an FDR of < 0.05. Next, Bedtools v2.27.1 (Quinlan & Hall, 2010) was used to identify significant loci that were unique (i.e. loci with non-overlapping borders) to a latent cognitive factor-SCZ pair. Genes were mapped to the unique significant loci using data provided by Ensembl (Cunningham et al., 2021) based on the GRCh38 reference genome. The GENE2FUNC function in FUMA was used to test for enrichment of the identified genes for each latent cognitive

factor-SCZ pair in gene sets obtained from MsigDB v7.0 (Liberzon et al., 2015). The Benjamini-Hochberg correction for multiple testing was applied per category of gene-sets.

5.3.9. Polygenic prediction of schizophrenia symptom dimensions

For PGS analyses, the target dataset comprised 306 individuals with SCZ and 1,060 controls of European ancestry from the Norwegian TOP Study (Engh et al., 2010). Briefly, the TOP study is an on-going case-control study based at Oslo University Hospital, Norway, that aims to investigate the clinical, genetic, neuroimaging, pharmacological and neurocognitive features of severe mental illness. For the current study, cases are defined as individuals with a DSM-IV diagnosis of schizophrenia, aged between 18-65 years, with the capacity to provide written informed consent. Individuals with pronounced cognitive deficits (IQ below 70), severe somatic illness, and brain damage were excluded from the study. Healthy controls are randomly selected from statistical records of individuals in the same catchment area as cases. Informed consent was provided by all participants and the human subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency. Further details of the recruitment and genotyping procedures for the TOP study are described in **Appendix 1**.

For individuals with SCZ in the TOP study, symptoms were measured using the positive, negative, and general psychopathology subscales of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) which has demonstrated good interrater reliability (Intraclass Coefficient = 0.82) in the TOP study (Rødevand et al., 2019). Mean scores for the PANSS in the TOP sample were 14.37 (SD = 5.29) for the positive scale, 15.30 (SD = 6.26) for the negative scale, and 12.95 (SD = 4.33) for the general psychopathology scale.

A PGS for each of the latent cognitive factors was calculated from the effect size estimates from the multivariate GWAS summary statistics using PRS-CS-auto (Ge et al., 2019). PRS-CS-auto is a Bayesian polygenic prediction method that estimates posterior effect sizes of SNPs by placing a continuous shrinkage prior on SNP effect sizes and incorporating information from an external LD reference panel. PRS-CS-auto automatically estimates the global shrinkage prior from the discovery dataset and does not require a validation dataset (Ge et al., 2019). In the present study, the 1000 Genomes Phase 3 release European sample (Abecasis et al., 2010) was used as the LD reference panel. SNPs with a MAF < 0.01 were excluded from the analysis, which left 964,446 SNPs for calculation of the PGS. Linear regression models were used to test the association between PGS for each latent cognitive factor with SCZ, and the three SCZ symptom dimensions. Age, sex, and the first 20 genetic principal components were included as covariates in the model. Phenotypic variance explained by the PGS (Nagelkerke's pseudo-R^2 for SCZ diagnosis and R^2 for PANSS subscale scores) was estimated as the difference between the R^2 of the full regression model (PGS and covariates) and the R^2 of the null model (covariates only). The Bonferroni correction was applied to account for multiple testing (α = 0.05/12 polygenic scores; $p < 4.17 \times 10^{-3}$).

5.4. Results

5.4.1. Genome-wide association analyses of UKB cognitive traits

The number of genome-wide significant loci identified for each cognitive trait ranged from 0 to 87 with the highest number of genome-wide significant loci observed for mean reaction time and no significant loci for paired associate learning and trail making – part B (**Figure 5.1**; **Appendix 2: Supplementary Table 5.1**). The LD score regression intercept for all univariate

GWAS was approximately 1 (range: 0.99-1.02), consistent with minimal inflation of the test statistic due to population stratification (Bulik-Sullivan et al., 2015b) (**Appendix 2: Supplementary Table 5.1**).

5.4.2. Estimations of SNP-based heritability and genetic correlations

The h^2_{SNP} for each cognitive trait and the genetic correlations between cognitive traits were estimated using LDSC. Estimates for h^2_{SNP} ranged from 3-22% for cognitive traits (**Figure 5.1**; **Appendix 2: Supplementary Table 5.1**). We observed positive genetic correlations between all cognitive traits (range 0.08–0.89, mean = 0.49, SD = 0.2; **Figure 5.2A**). All genetic correlations were significant (α = 0.05/66 pairs of traits; $p < 7.58 \times 10^{-4}$) with the exception of the correlations between mean reaction time and PAL (r_g = 0.11, SE = 0.04, $p = 5.3 \times 10^{-3}$), mean reaction time and numeric memory (r_g = 0.07, SE = 0.03, $p = 1.74 \times 10^{-2}$), and TMT-A and PAL (r_g = 0.25, SE = 0.09, $p = 6.2 \times 10^{-3}$). A hierarchal clustering algorithm was applied to the genetic correlation matrix and three distinct clusters of cognitive phenotypes were identified. The first cluster included Pairs Matching, TMT-A, TMT-B, Symbol Digit Substitution and Tower Rearranging, the second cluster included Fluid Intelligence, Numeric Memory, Prospective Memory, Matrix Reasoning, and PAL, and the third cluster comprised of mean reaction time and RTV (**Figure 5.2B**).

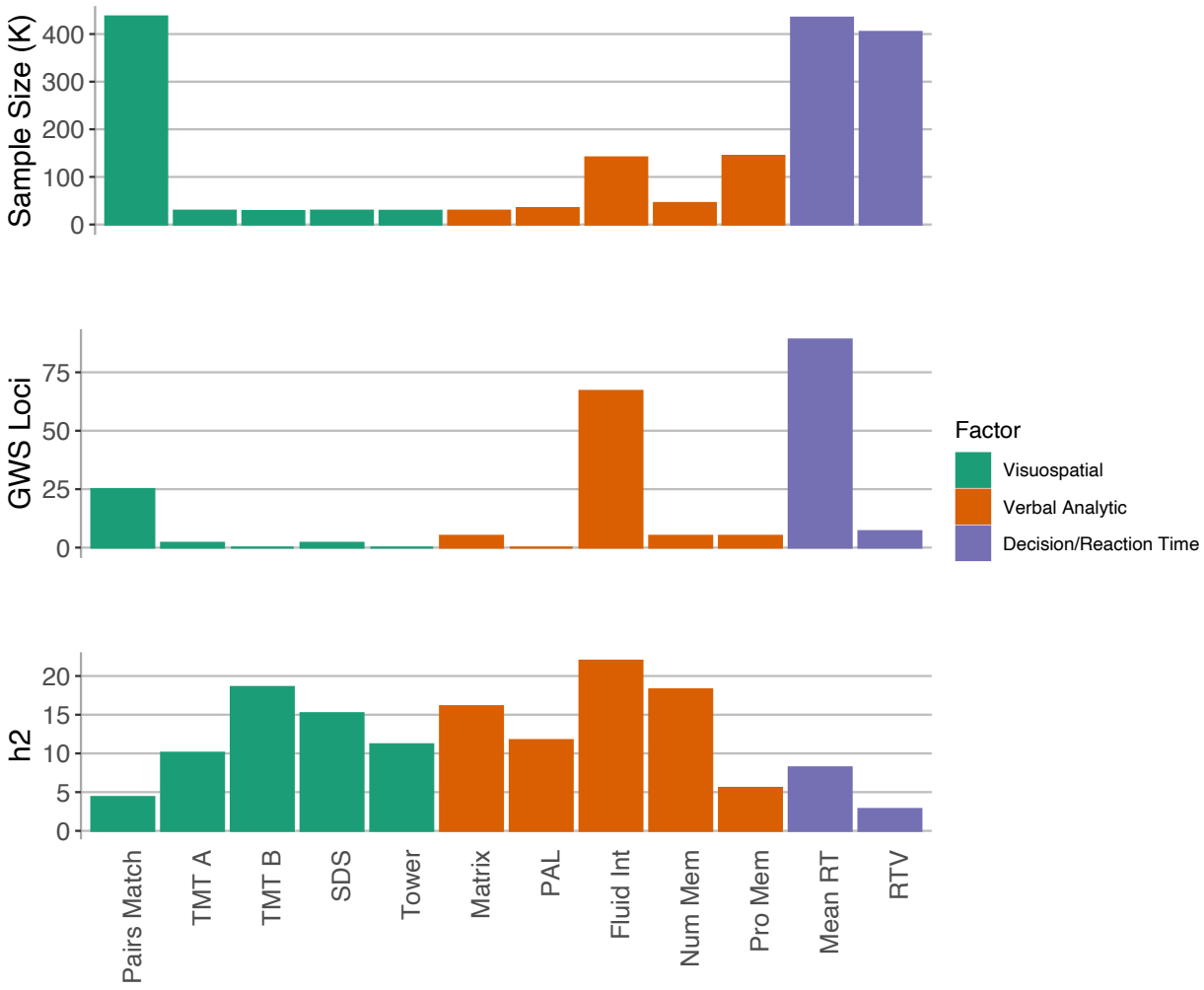

Figure 5. 1: Overview of Univariate GWAS for UKB Cognitive Traits

Bar chart illustrating the sample size, number of genome-wide significant loci, and SNP-based heritability estimates for univariate GWAS of 12 cognitive traits from the UK Biobank. Traits are colour-coded according to the three-factor model derived using Genomic Structural Equation Modelling. Pairs Match, Pairs Matching; TMT A, Trail Making Test-Part A; TMT B, Trail Making Test-Part B; SDS, Symbol Digit Substitution; Tower, Tower Rearranging; Matrix, Matrix Pattern Completion; PAL, Paired Associate Learning; Fluid Int, Fluid Intelligence; Num Mem, Numeric Memory; Pro Mem, Prospective Memory; Mean RT, Mean Reaction Time; RTV, Reaction Time Variability.

5.4.3. Genomic structural equation modelling

The genetic covariance matrix for the 12 UKB cognitive traits was modeled using Genomic SEM. First, a single common factor model in which the single latent factor represented a genetic *g* factor was explored. Model fit was suboptimal for the single common factor model (chi-square, $\chi2(54) = 2106.75$, AIC = 2154.75, CFI = 0.71, SRMR = 0.12; **Appendix 2: Supplementary Table 5.2 and Supplementary Figure 5.1**). Next, it was investigated whether a correlated two- or three-factor model closely approximated the observed genetic covariance matrix. Consistent with the results from the hierarchal clustering of the genetic correlation matrix, it was found that a three correlated factors model fit the data best (chi-square, $\chi2(49) = 320.72$, AIC = 378.72, CFI = 0.96, SRMR = 0.07; **Figure 5.2B**; **Appendix 2: Supplementary Table 5.2**). In the three-factor model, factor 1 and factor 2 exhibit the highest genetic correlation among the cognitive factors ($r_g = 0.65$, SE = 0.02, $p = 2.59 \times 10^{-215}$) and these factors may be conceptualized as capturing cognitive traits related to the broad cognitive ability, fluid reasoning (Flanagan & Dixon). Factor 1 is primarily defined by cognitive phenotypes that relate to visuospatial aspects of fluid reasoning and includes Pairs Matching, TMT-A, TMT-B, Symbol Digit Substitution and Tower Rearranging. Factor 2 largely captures measures that assess the verbal analytic component of fluid reasoning and is defined by Fluid Intelligence, Numeric Memory, Prospective Memory, Matrix Reasoning, and PAL. Factor 3 is characterized by cognitive phenotypes related to the broad cognitive ability, "decision/reaction time/speed" (Flanagan & Dixon). The cognitive traits, mean reaction time and RTV load on the third factor, which is less correlated with factor 1 ($r_g = 0.37$, SE = 0.03, $p = 2.75 \times 10^{-42}$) and factor 2 ($r_g = 0.29$, SE = 0.02, $p = 3.44 \times 10^{-37}$).

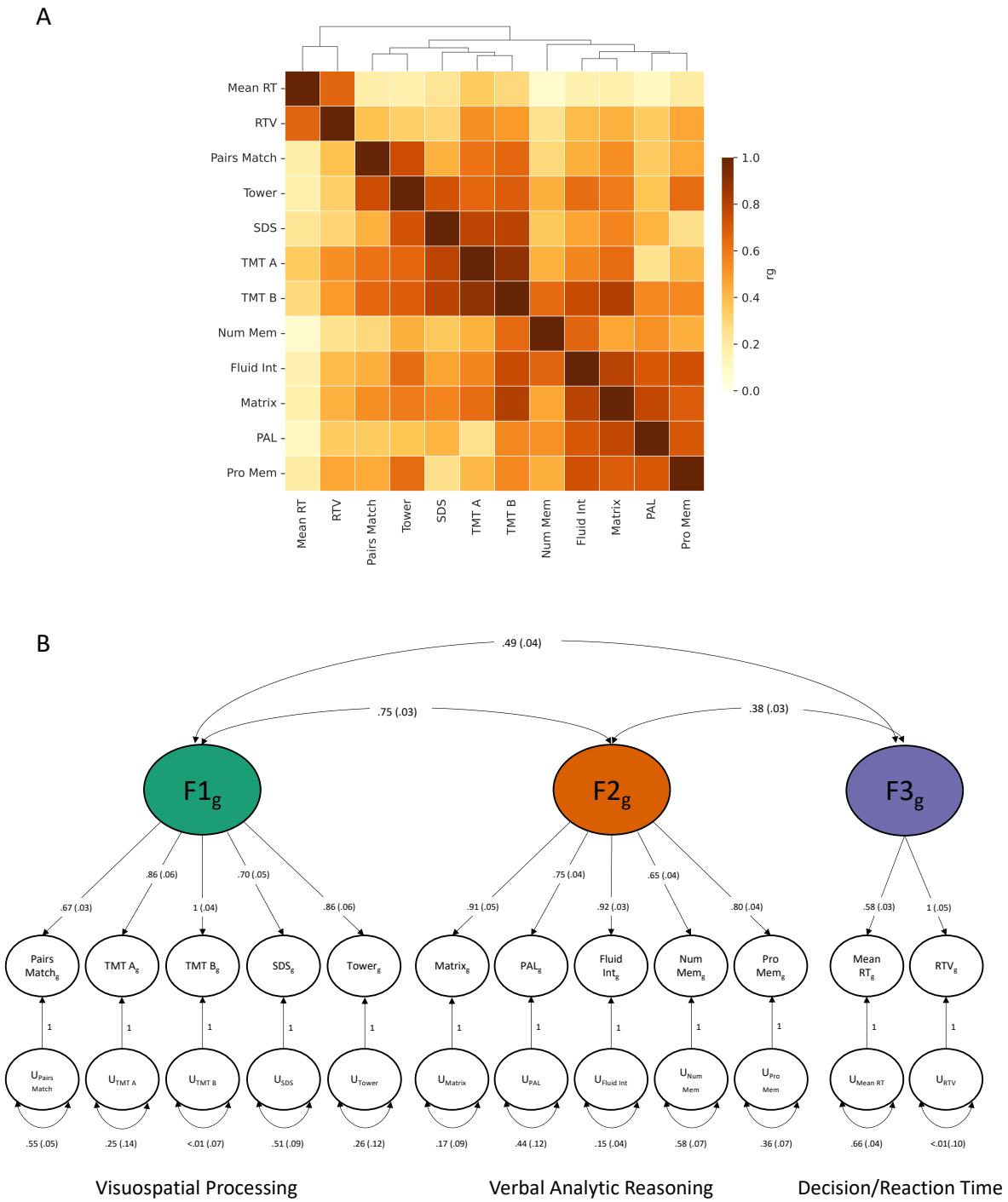

Figure 5. 2: Multivariate Structure of 12 Cognitive Traits from the UK Biobank

(**A**) Heatmap showing genetic correlations estimated using LDSC. (**B**) Path diagram showing standardized results from the correlated three-factor model. Circles represent latent variables that are inferred from the data. Single-headed arrows depict regression relationships with the arrows pointing from the independent variables to the dependent variables. Two-headed arrows represent covariance relationships between variables or the

residual variance of a variable if the arrow connects the variable to itself. Standard errors of the estimates are in parenthesis. Pairs Match, Pairs Matching; TMT A, Trail Making Test-Part A; TMT B, Trail Making Test-Part B; SDS, Symbol Digit Substitution; Tower, Tower Rearranging; Matrix, Matrix Pattern Completion; PAL, Paired Associate Learning; Fluid Int, Fluid Intelligence; Num Mem, Numeric Memory; Pro Mem, Prospective Memory; Mean RT, Mean Reaction Time; RTV, Reaction Time Variability.

5.4.4. Multivariate GWAS

I conducted multivariate GWASs of the three latent cognitive factors using Genomic SEM. The effective sample size ranged from 160,729 for factor 2 (verbal analytic reasoning) to 637,271 for factor 1 (visuospatial processing) (**Table 5.1**). Substantial inflation of the test statistic was observed for all latent cognitive factors (**Appendix 2: Supplementary Figure 5.2**) however LD score regression intercepts were 1, suggesting that test-statistic inflation reflects high polygenicity and not other sources of bias (**Table 5.1**).

Table 5. 1: Summary of Multivariate GWAS Results

Multivariate GWAS Target	Effective *n*	GWS SNPs	GWS Loci	LDSR Intercept
Factor 1 (visuospatial processing)	637,271	1000	12	1.02
Factor 2 (verbal analytic reasoning)	160,729	5846	77	1.00
Factor 3 (decision/reaction time)	597,828	1455	32	0.99

5.4.5. Estimation of genetic overlap between cognitive factors and schizophrenia

There was a significant negative genetic correlation between all three latent cognitive factors and SCZ (**Appendix 2: Supplementary Table 5.3**). Bivariate MiXeR demonstrated substantial polygenic overlap between each latent cognitive factor and SCZ, beyond that captured by estimates of genetic correlation (**Figure 5.3**). Of the 9,600 variants predicted to influence SCZ, almost all variants were also predicted to influence the latent cognitive factors. Notably, factor 1 (visuospatial processing) demonstrated the greatest negative global genetic correlation with SCZ (rg = -0.38, SE = 0.025, p = $9x10^{-52}$) and the greatest percentage of shared variants (63%) with a discordant effect on a latent cognitive factor and SCZ (**Figure 5.3**).

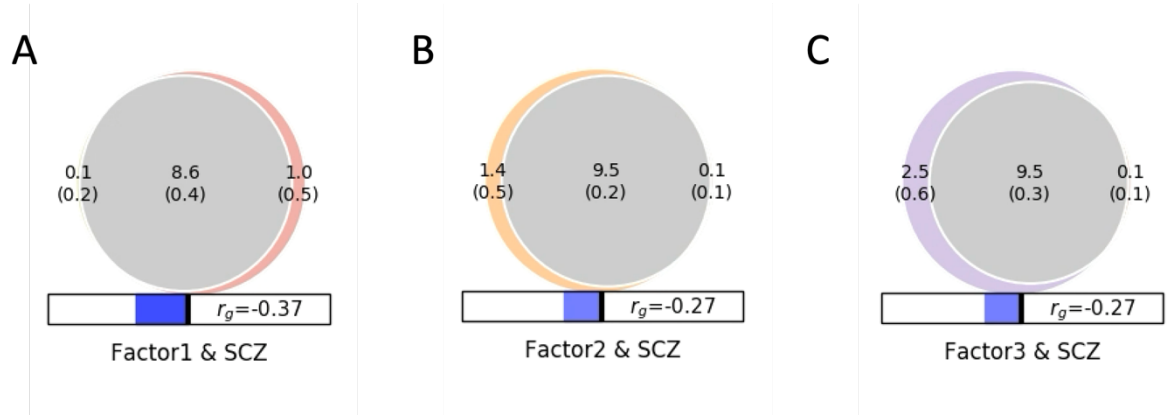

Figure 5. 3: Bivariate MiXeR Results

(**A**) Polygenic overlap between latent cognitive factor 1 (visuospatial processing) and schizophrenia. (**B**) Polygenic overlap between latent cognitive factor 2 (verbal analytic reasoning) and schizophrenia. (**C**) Polygenic overlap between latent cognitive factor 3 (decision/reaction time) and schizophrenia. Venn diagram shows the number (in thousands) of estimated causal variants shared between both traits (grey) and unique to each trait (in colour). Standard deviations of the estimates are shown in parenthesis. The size of the circle represents the extent of polygenicity of each trait.

I employed LAVA to explore regional patterns of genetic correlation between the latent cognitive factors and SCZ. The number of genetic regions that were significantly heritable ($p < 2.00x10^{-5}$) for SCZ and a latent cognitive factor ranged from 149-170 (**Appendix 2: Supplementary Table 5.4**). Among the significantly heritable regions, the number of regions with a significant genetic correlation (α = 0.05/number of significantly heritable regions for both traits) between SCZ and a latent cognitive factor ranged from 6-21. Most significant local genetic correlations were negative (**Figure 5.4**; **Appendix 2: Supplementary Table 5.5**) with the exception of a positive correlation between SCZ and factor 2 (verbal analytic reasoning) at 2 loci [chr 3: 47588462-50387742, chr 12: 77800464-79315178] (**Appendix 2: Supplementary Table 5.5**).

As shown in **Figure 5.5**, conjFDR analysis demonstrated that SCZ shares loci with cognitive factor 1 (N=93), cognitive factor 2 (N=267), and cognitive factor 3 (N=175). Consistent with results from bivariate MiXeR analysis, factor 1 shared the lowest number of loci with SCZ. Among the shared associations with SCZ, 46 were unique to cognitive factor 1, 189 were unique to factor 2, and 113 were unique to factor 3.

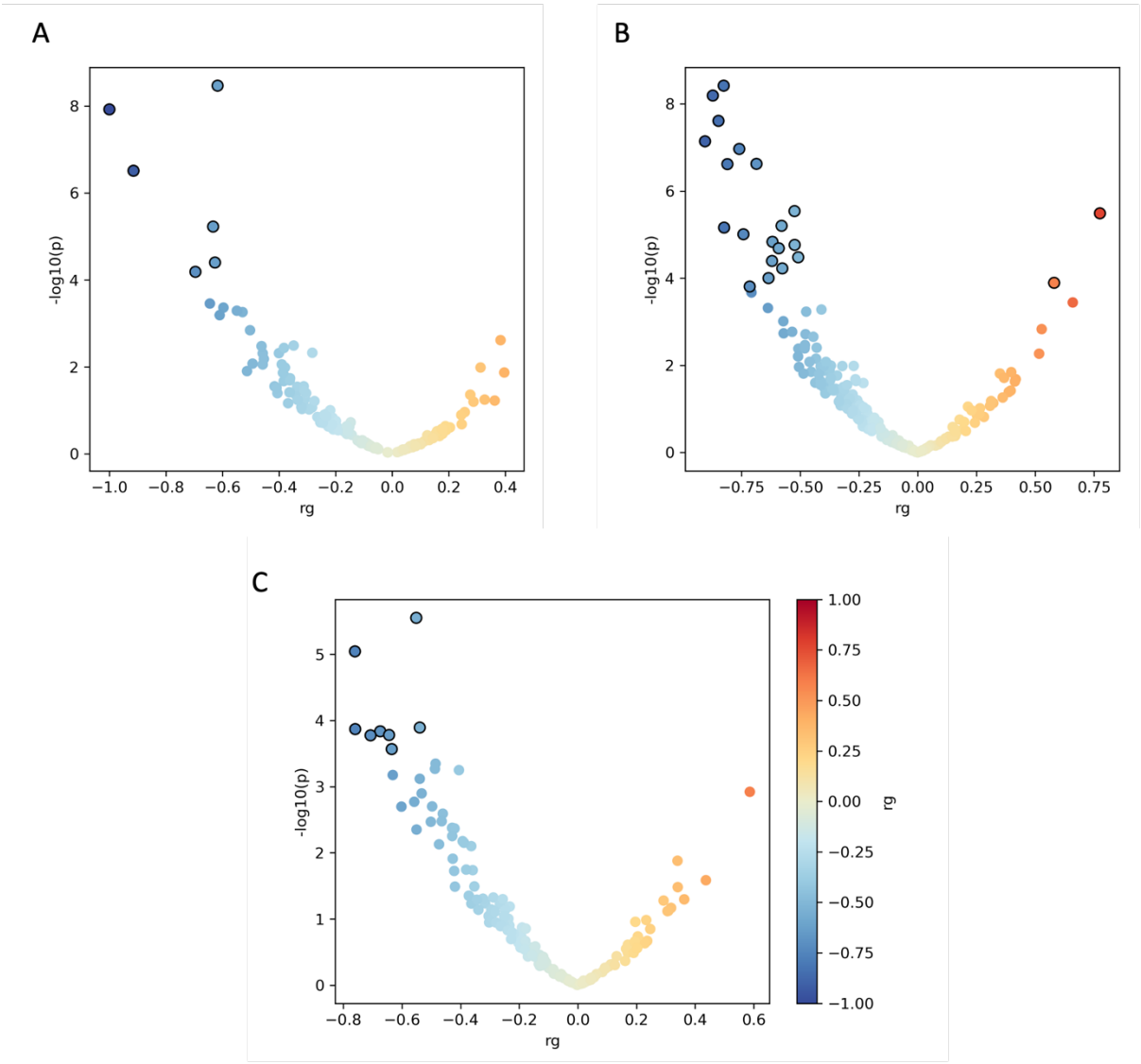

Figure 5. 4: Volcano Plots Showing Local Genetic Correlations Between Schizophrenia and Latent Cognitive Factor 1 (A), Factor 2 (B), and Factor 3 (C)

Local genetic correlations for regions with significant heritability for schizophrenia and the latent cognitive factor are represented as a single point. Regions with a significant genetic correlation after Bonferroni correction are outlined in black.

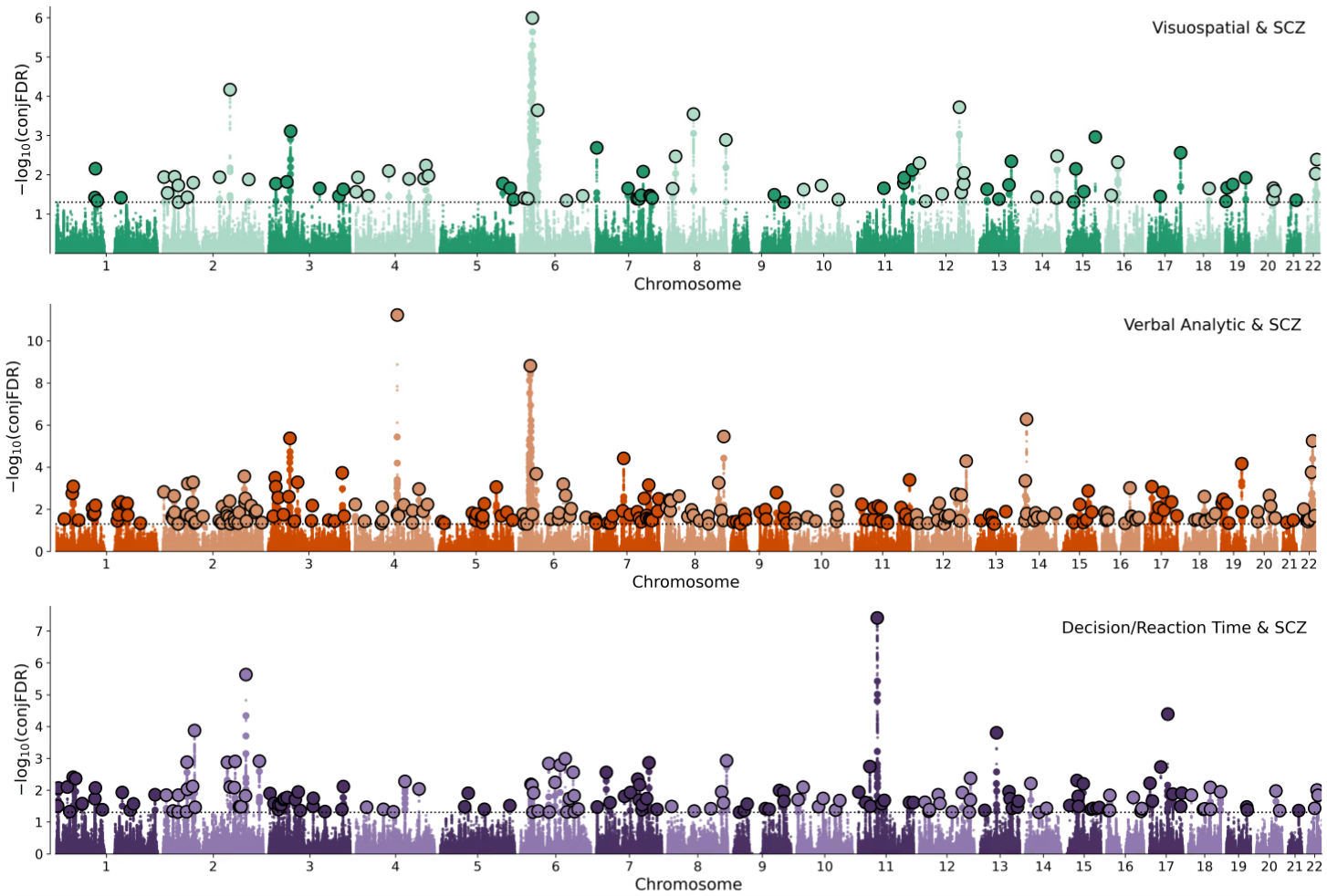

Figure 5. 5: Discovery of Loci Jointly Associated with Each Latent Cognitive Factor and Schizophrenia

Manhattan plots showing the -$\log_{10}$ transformed conjFDR values for a joint association with a latent cognitive factor and schizophrenia (SCZ) for each SNP (y-axis) plotted against chromosomal position (x-axis). The dotted line indicates the significance threshold (conjFDR < 0.05). Lead SNPs are outlined in black and independent significant SNPs are represented by larger circles.

5.4.6. Functional annotation of identified loci

The genes mapped to unique significant loci for each latent cognitive factor-SCZ pair are listed in **Appendix 2: Supplementary Tables 5.6-5.8**. For the unique significant loci shared between cognitive factor 1 (visuospatial processing) and SCZ, gene-set analysis for cellular components demonstrated significant results for the synapse (FDR = 1.39×10^{-2}), the synaptic membrane (FDR = 3.05×10^{-2}), the postsynaptic membrane (FDR = 3.05×10^{-2}), neurons (FDR = 3.05×10^{-2}), and neuron projections (FDR = 4.80×10^{-2}) and no significant gene-sets for biological processes (**Appendix 2: Supplementary Table 5.9**). For unique significant loci associated with cognitive factor 2 (verbal analytic reasoning) and SCZ, gene-set analysis revealed significant results for genes involved in axon guidance (FDR = 2.02×10^{-2}) and cell adhesion via plasma adhesion molecules (FDR = 1.49×10^{-3}) (**Appendix 2: Supplementary Table 5.10**). Lastly, the genes mapped to unique significant loci associated with latent cognitive factor 3 (decision/reaction time) and SCZ were significantly enriched for two gene-sets involved in neuronal development: regulation of neuron differentiation (FDR = 4.22×10^{-2}) and regulation of neuron projection development (FDR = 4.22×10^{-2}) (**Appendix 2: Supplementary Table 5.11**).

5.4.7. Polygenic prediction of schizophrenia symptom dimensions

I created PGS for the three latent cognitive factors and tested the ability of each cognitive factor-PGS to predict SCZ and SCZ symptom domains in individuals from the TOP study. There was a significant association between SCZ diagnosis and the PGS for latent cognitive factor 1, visuospatial processing ($R^2 = 0.026$, $p = 2.48 \times 10^{-6}$), and latent cognitive factor 2, verbal analytic reasoning ($R^2 = 0.011$, $p = 1.80 \times 10^{-3}$) (**Figure 5.6**). There were no significant

associations found between any of the PGS for the latent cognitive factors and SCZ symptom dimensions (**Figure 5.6**; **Appendix 2: Supplementary Table 5.12**).

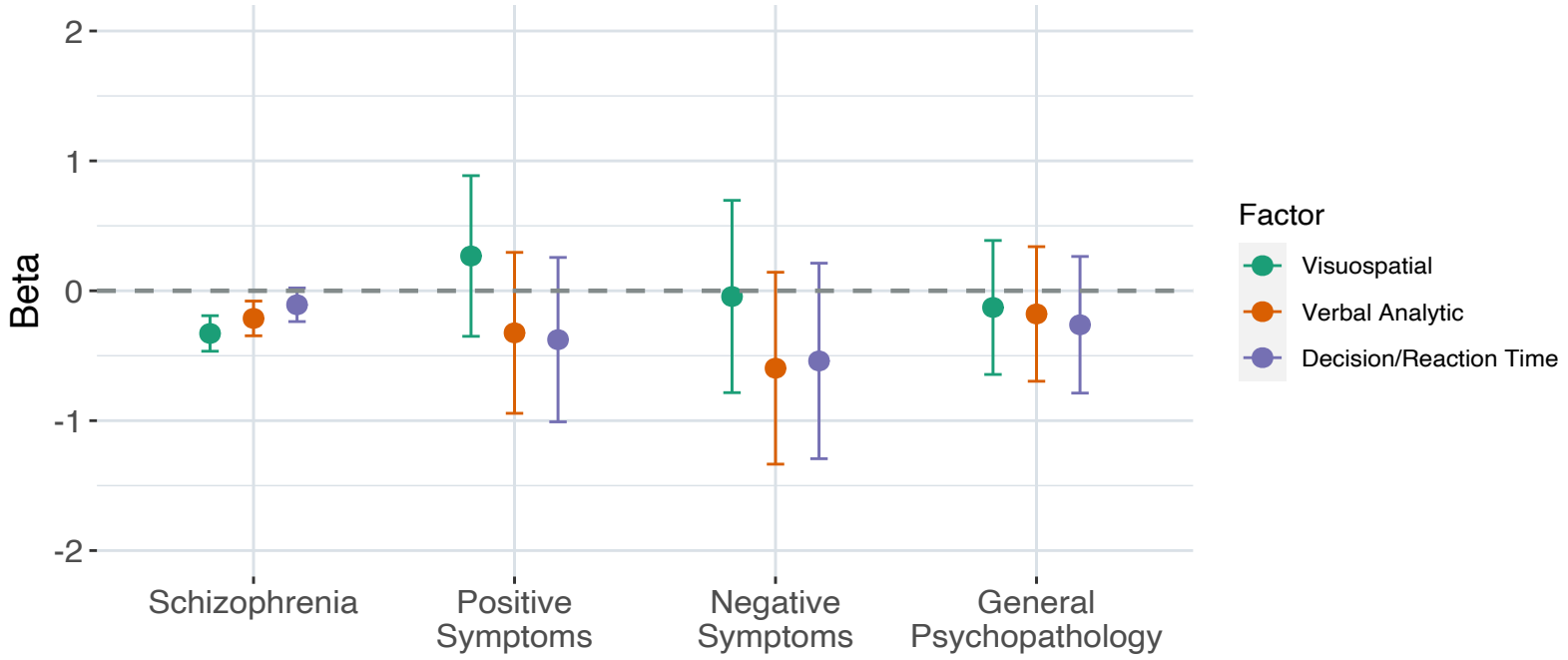

Figure 5. 6: Association of Polygenic Scores for Each Latent Cognitive Factor with Schizophrenia and Three Schizophrenia Symptom Dimensions

Associations of polygenic scores (PGS) for each latent cognitive factor with schizophrenia, and schizophrenia symptom dimensions (negative, positive, and general psychopathology) in individuals from the TOP study. Point estimates for beta values are shown with 95% confidence intervals. The dotted line represents a null model.

5.5. Discussion

The main aim of this chapter was to investigate the common genetic determinants shared between SCZ and cognitive function using three latent factors that captured the genetic covariance structure of 12 cognitive measures from the UKB. The results showed substantial polygenic overlap between SCZ and the genetically determined latent cognitive factors. All three latent cognitive factors exhibited a negative genetic correlation with SCZ that was largely consistent for both global and local patterns of genetic correlation. Biological annotation of the loci jointly associated with SCZ and the latent cognitive factors implicated genes involved in the development and functioning of the central nervous system. Additionally, it was demonstrated that PGS for the latent cognitive factors were not predictive of schizophrenia symptoms, suggesting distinctions in the underlying genetic architecture of cognitive function and phenotypic dimensions in schizophrenia.

Genomic SEM was applied to GWAS summary statistics for 12 cognitive measures in the UKB and it was found that a three-factor model best explained the genetic correlations between the cognitive traits. This is consistent with findings from a previous study that applied structural equation modeling to phenotypic data from the UKB cognitive assessments and found that a three-factor solution fit the data best (Ciobanu et al., 2023). The three cognitive factors identified in the current study may be characterized using the framework provided by the Cattell-Horn-Carrol (CHC) theory of human cognitive abilities, which proposes a three-stratum model of human intelligence (Flanagan & Dixon; Schneider & McGrew, 2018). Consistent with the relatively high genetic correlation between factor 1 and factor 2, the first 2 latent cognitive factors appear to capture the same broad cognitive ability, fluid reasoning (*Gf*). However, factor 1 is largely defined by cognitive traits that capture visuospatial

processing whereas factor 2 is defined by cognitive tests that measure verbal analytic reasoning. Factor 3 is less genetically correlated with the first 2 factors and measures a distinct cognitive ability, decision/reaction time/speed (*Gt).* The convergence of the genetic and phenotypic factor structures for the UKB cognitive traits suggests that the existing phenotypic structure is rooted in the genetic underpinnings of the traits.

Consistent with the literature, all three latent cognitive factors demonstrated a significant negative genetic correlation with the diagnosis of SCZ with the greatest negative correlation observed between the visuospatial factor (factor 1) and SCZ. The genetic correlation between the visuospatial factor and SCZ is of greater magnitude than that reported for general cognitive ability and SCZ (r_g = -0.23) (Davies et al., 2018). This finding suggests that we may be missing unique patterns of genetic association between SCZ and cognitive abilities when using one broad measure of cognitive function. Patterns of local genetic correlation between the latent cognitive factors and SCZ were generally consistent with global genetic correlations. These findings indicate that, in general, genetic liability for SCZ has a negative effect on cognitive abilities and that the phenotypic relationship between SCZ and cognitive impairment has a genetic basis. LAVA analysis revealed that most significantly heritable regions demonstrated a negative association between the cognitive factors and SCZ and that most significant regional genetic correlations were negative. One of the regions that showed a positive genetic correlation between the verbal analytic factor and SCZ was located on chromosome 3 (Chr3p21). This region is enriched for genes that have been associated with intelligence and general cognitive ability in previous GWAS (Coleman et al., 2019; Davies et al., 2018). Further research is required to explore the relationship between genes in this region and cognitive function in SCZ.

Results from bivariate MiXeR and conjFDR analysis converged with each cognitive factor demonstrating substantial polygenic overlap with SCZ. Notably, the visuospatial factor demonstrated the greatest genome-wide genetic correlation with SCZ despite conjFDR showing that this factor shared the lowest number of loci with SCZ. These findings demonstrate that a large genetic correlation does not necessarily correspond to the greatest overlap in genetic architecture. Instead, these findings imply that the variants that are shared between the visuospatial factor and SCZ demonstrate a more consistent direction of effect for the two traits than those shared between the other latent cognitive factors and SCZ. The conjFDR analysis showed that the majority of loci found to be jointly associated with each latent cognitive factor-SCZ pair were unique to the pair. Given the almost complete overlap between the genetic risk loci of each cognitive factor and SCZ demonstrated by bivariate MiXeR, the difference in significant loci shared between each cognitive factor and SCZ is unlikely to reflect a unique set of variants associated with each cognitive factor. Instead, this result indicates that despite all cognitive factors sharing most causal variants, the magnitude and potentially direction of effects of these shared variants vary between the latent cognitive factors. The unique significant loci for each latent cognitive factor-SCZ pair were annotated and gene-set enrichment analysis was conducted to explore putative biological mechanisms underlying the association between cognitive abilities and SCZ. Gene-set enrichment analysis implicated distinct gene-sets for each latent cognitive factor-SCZ pair but converged on processes and cellular components related to neurodevelopment and neuronal function. This is consistent with previous reports that have found that loci shared between SCZ and intelligence implicated genes involved in neurodevelopment, synaptic integrity, and neurotransmission (Smeland et al., 2020a).

A further objective of this chapter was to understand the relationship between genetic liability to broad dimensions of cognitive function and SCZ symptoms. A PGS for each latent cognitive factor was calculated and the ability of the PGS to predict SCZ as well as positive symptoms, negative symptoms, and general psychopathology in individuals with SCZ was assessed. The visuospatial factor PGS and verbal analytic factor PGS significantly predicted SCZ but there were no significant associations between any latent cognitive factor PGS and SCZ symptoms. Previous research has consistently demonstrated a significant relationship between PGS for general cognitive ability and SCZ however, findings on the relationship between PGS for specific cognitive abilities and SCZ are mixed (Hubbard et al., 2016; Lencz et al., 2014). The lack of consistent results may be due to differences in the methods of assessing and defining cognitive abilities or domains and a consensus on the measurement of cognitive domains would improve comparability across studies. The lack of association between PGS for the latent cognitive factors and SCZ symptoms is in keeping with results from a previous study which found no association between an intelligence PGS and positive, negative, and disorganized symptoms in SCZ (Legge et al., 2021). These findings suggest that there is distinction in the genetic influences on cognitive abilities and other symptoms of SCZ and extend findings from phenotypic analyses that show minimal association between positive and negative symptoms and cognitive impairment in SCZ (McCutcheon et al., 2023).

The results of the current study should be interpreted in the context of several limitations. First, the cognitive assessments from the UKB are brief and bespoke. While previous studies have demonstrated that the psychometric properties for most assessments are adequate (Lyall et al., 2016; Ritchie et al., 2014), the findings of the current study require replication in

other samples with psychometrically valid measures of cognitive function. Second, the sample sizes and heritability estimates for the cognitive traits differed. Thus, differences in power for the univariate GWAS, defining each factor, may have affected the results of the multivariate GWAS for each factor. Third, the mean scores for the subscales of the PANSS were relatively low, which is expected given that the TOP study limited enrolment to individuals with the capacity to provide informed consent. As the PANSS assesses current symptom severity, a lifetime measure of schizophrenia symptoms may have been more appropriate for assessing the relationship between cognitive abilities and schizophrenia symptoms. Lastly, the analyses was restricted to individuals of European ancestry and the results may not be generalizable to other populations. Efforts to improve the representation of diverse global populations in genomic studies are ongoing (Hindorff et al., 2018; Martin et al., 2022) and once the relevant large scale datasets for non-European populations become available, the generalizability of the results from the current study should be examined.

5.6. Conclusion

In summary, three genetically determined correlated cognitive factors were estimated, and a variety of genomic methods were employed to investigate the relationship between these cognitive factors and SCZ. There was extensive polygenic overlap between the latent cognitive factors and SCZ and it was found that most shared common genetic variants have opposite directions of effect on cognitive abilities and SCZ risk. This study demonstrated that most loci shared between the latent cognitive factors and SCZ show unique patterns of association with each cognitive factor. Results from biological annotation of shared loci converged and implicated biological processes related to neurodevelopment and neuronal functioning. Lastly, the polygenic score analyses showed a distinction in the common genetic determinants

of cognitive abilities and SCZ symptoms. Collectively, the results suggest that heterogeneity in the extent of cognitive impairment observed across cognitive domains in SCZ reflects differences in genetic risk sharing between specific cognitive domains and SCZ.

Chapter 6: General Discussion and Conclusions

This chapter includes an overview and synthesis of the key findings of this thesis, a discussion of the scientific relevance of this body of work, and the implications for future research.

6.1. Summary of findings

The overarching aim of this thesis was to extend current understanding of cognitive impairment in SCZ by using previously under-researched or novel metrics of cognitive performance. To address this aim, this thesis includes three studies that use cognitive and genetic data from 2 deeply phenotyped case-control studies of SCZ, The SAX and TOP studies, and one of the largest existing biobanks, The UKB. The thesis begins with a narrative review of the key literature related to WIV in cognitive performance in SCZ. This is followed by study of the demographic and clinical predictors of WIV in SCZ in the SAX study. Next, the largest GWAS to date of RTV, an index of across-trial WIV, is presented accompanied by an investigation of the functional significance of identified variants as well as the genetic correlation between RTV and selected neuropsychiatric traits. Lastly, a data driven approach is used to derive genetic factors corresponding to broad cognitive abilities and the genetic overlap between these latent cognitive factors, SCZ, and SCZ symptom dimensions is assessed.

Chapter 2 begins with an overview of the neurobiological underpinnings and clinical significance of WIV in cognitive performance in SCZ and establishes the rationale for further study of this metric of cognitive function. Evidence from the review suggests that although abnormalities in WIV are present in many neuropsychiatric disorders, elevations in WIV are a

sensitive indicator of psychopathology even when mean performance measures on cognitive tests are normal. The relative ease of measurement and potential to calculate WIV from existing datasets enhance the utility of WIV as a predictor of psychosis risk in healthy populations and of functional outcomes in people with psychosis. The review elaborates on the established neurological underpinnings of WIV in SCZ - including abnormal white matter integrity, functional connectivity, and dopaminergic activity in the disorder. Notably, the review identifies that studies on the genetic underpinnings of WIV are sparse and primarily limited to candidate gene studies. Given the relative ease of measurement of WIV, it is an appealing phenotype for large GWAS.

The aim of Chapter 3, the first empirical chapter of the thesis, was to characterize individual differences in WIV and its clinical significance in SCZ using data from the SAX study. Firstly, the results show that WIV across measures of performance speed in a battery of cognitive tests was associated with a diagnosis of SCZ, with PSZ having increased speed WIV compared to controls. Second, the investigation of the predictors of WIV in PSZ revealed that increased speed WIV was associated with older age, lower level of education, and lower GAF scores. Increased accuracy WIV was only associated with younger age and appears to be a less sensitive marker of cognitive dysfunction amongst PSZ. The findings from this analysis are generally consistent with those from studies of WIV in high income settings and demonstrate that despite the difference in educational levels, prevalence of comorbid conditions, and treatment practices, the significant predictors of WIV are comparable. In summary, the findings from Chapter 3 provide support for the use of WIV as an index of cognitive impairment in SCZ and highlight the potential for future research using measurements of WIV to extend our understanding of cognitive impairment in SCZ.

In Chapter 4 of the thesis, the contributions of common genetic variants to WIV, as measured by RTV, were explored. Data from 404,302 participants in the UKB was used to conduct the largest GWAS of RTV to date. RTV was found to have a significant h^2_{SNP} and was significantly associated with 162 genome-wide significant SNPs distributed across 7 genomic loci. The genes associated with the identified loci implicated genes involved in neural development and synaptic function. Additionally, the finding of significant genetic correlations between RTV and SCZ, educational attainment, and general cognitive ability suggests that the phenotypic association of RTV with these traits has a genetic basis. Lastly, evidence for replicability of the results from the discovery GWAS was provided through PGS analysis. A RTV-PGS was calculated from the discovery GWAS and it was demonstrated that the PGS was able to significantly predict RTV in independent samples. However, consistent with the literature, it was found that the predictive ability of the RTV-PRS declined when the ancestry of the target cohort differed to that of the discovery cohort. Collectively, the results of Chapter 4 further current understanding of the common genetic architecture of RTV and may be leveraged by future studies to gain novel insights into the biological underpinnings of related complex disorders, like SCZ.

The aim of Chapter 5 was to investigate the overlap in the common genetic underpinnings of cognitive function and SCZ. Genomic SEM revealed that a three-factor model best explained the genetic covariance between 12 cognitive traits measured in the UKB. The three latent factors corresponded to broad cognitive abilities, namely visuo-spatial processing, verbal analytic reasoning and decision/reaction time. There was evidence of substantial polygenic

overlap between the latent cognitive factors and SCZ and it was found that most shared common variants have opposite directions of effects on cognitive abilities and SCZ risk. Furthermore, the study revealed that while all latent cognitive factors shared a majority of their causal variants, the magnitude and direction of effects of these shared variants varied between the cognitive factors. This resulted in a unique set of loci that reached significance for a joint association with a cognitive factor-SCZ pair. Despite differences in patterns of association between the variants and each cognitive factor, biological annotation of the unique significant loci showed that across factors, the shared loci with SCZ implicated biological processes and cellular components related to neurodevelopment and neuronal function. Lastly, using PGS analysis, differences in the common genetic architecture of cognitive abilities and SCZ symptoms were demonstrated. Overall, the results of Chapter 5 suggest that differences in genetic risk sharing between specific cognitive abilities and SCZ may contribute to the variation in degree of impairment across cognitive domains in the disorder.

6.2. Emerging Themes

This thesis provided several key insights into cognitive performance in SCZ, which may be summarised by the following three overarching themes:

6.2.1. Variability in performance across cognitive domains in schizophrenia

Previous research has established that while PSZ demonstrate a global deficit in cognitive performance, the extent of impairment varies across cognitive domains. This thesis provides further evidence of differential impairment by demonstrating increased WIV for both accuracy and speed measures across a battery of cognitive tasks in PSZ compared to healthy

controls in the SAX study. However, it was observed that the relationship between accuracy WIV and a diagnosis of SCZ was non-significant in the SAX sample. Studies of cognitive ageing have shown that speed based measures of WIV are better able to predict cognitive impairment than accuracy based measures (Christ et al., 2018; Hultsch et al., 2000). The findings of this thesis are consistent with this observation but are the first to extend this finding to a sample of PSZ.

The results of the genetic analyses suggest that the phenotypic differences in performance across cognitive domains in SCZ are underpinned by differences in the genetic architecture of cognitive abilities. The investigation of the genetic overlap between three latent cognitive factors and SCZ revealed that although the cognitive factors shared most causal variants, the strength and direction of effect of these variants varied across the cognitive factors. Consequently, there were differences in the genetic loci that reached significance for a shared association with SCZ and each cognitive factor. These results provide evidence that the study of the overlap in the genetic underpinnings of cognitive function and SCZ may benefit from accounting for the heterogeneity that is observed on both a phenotypic and genetic level. Further studies are required to delineate the shared genetic architecture of specific domains of cognitive function and SCZ.

6.2.2. Overlap in the genetic determinants of cognitive function and schizophrenia

Two of the studies included in this thesis provide evidence of overlap in the genetic underpinnings of cognitive function and SCZ. The results show that the common genetic determinants of cognitive function, whether assessed using WIV or broad cognitive abilities,

are significantly correlated with the common genetic determinants of SCZ. Additionally, the results indicate that the variants that are associated with increased genetic risk of SCZ are associated with worse cognitive performance. This finding is largely in keeping with previous research on the shared genetic architecture of SCZ and cognitive ability (Mallet et al., 2020; Smeland et al., 2020a)

Functional annotation of the results from the RTV-GWAS revealed that the genes associated with RTV are related to neural development and synaptic function. The biological processes underpinning RTV converged with those that have been implicated in common and rare variant studies of the genetics of SCZ (Singh et al., 2022; Trubetskoy et al., 2022). Further, genes associated with loci shared between the genetically determined cognitive factors and SCZ were over represented in gene-sets related to neurodevelopment and neuronal function. Collectively, these results implicate these processes in the biology of cognitive impairment in SCZ and may be used to inform future studies aiming to derive mechanistic insights.

6.2.3. The genetic determinants of cognitive function are different to those of other symptoms in schizophrenia

Cognitive dysfunction is considered a key feature of SCZ but evidence from phenotypic analyses suggests that cognitive symptoms form a distinct symptom cluster in the disorder (Moura et al., 2021; Rodriguez-Jimenez et al., 2013). This distinction appears to be rooted in genetic differences as previous research has failed to find an association between the genetic underpinnings of cognitive function and positive, negative, and disorganized symptoms in the disorder (Legge et al., 2021). This thesis builds on existing knowledge by providing the first evidence that the common genetic determinants of 3 broad cognitive abilities are distinct

from those of positive, negative, and general psychopathological symptoms in SCZ. The finding of heterogeneity in the genetic underpinnings of SCZ symptom dimensions provides support for research that transcends classic psychiatry nosology and investigates the neurobiology of specific symptom dimensions.

6.3. Limitations and Future Considerations

The work described in this thesis has advanced current understanding of cognitive function in SCZ. However, each study had limitations and there are several areas that warrant further exploration in future research.

6.3.1. The contribution of rare variants to cognitive function

This thesis focused on the contribution of common genetic variation to cognitive function and identified several genotype-phenotype associations using a genome-wide approach. However, it is known that rare genetic variants contribute towards cognitive function and explain a substantial portion of the genetic variation in the trait (Chen et al., 2023; Young & Martin, 2023). The increasing availability of whole-exome sequencing and whole-genome sequencing data provides an opportunity for further investigation of rare variant associations with cognitive function. For example, a recent exome-wide association study using data from the UKB identified genes that are associated with cognitive function in the general population through rare coding mutations with large effects (Chen et al., 2023). An extension of this approach to other populations, for example people with SCZ, may allow for the identification of genes that are associated with cognitive dysfunction in the disorder. Additionally, a major limitation of GWAS is that it is challenging to identify causal genes for a trait from the many common variant associations (Edwards et al., 2013). The identification of genes affected by

rare variants associated with a trait, such as cognitive function, may facilitate the prioritization of causal genes from GWAS (Backman et al., 2021; Chen et al., 2023). Lastly, the findings of Chen et al. (2023) imply that an individual's polygenic background may modulate the penetrance of rare damaging mutations and the resulting phenotypic outcomes. Similarly, it has been shown that common genetic variants modify the phenotypic expression of rare variants known to be associated with neurodevelopmental disorders (Niemi et al., 2018). Further research is required to delineate the interaction between common and rare variants and the cumulative impact of common and rare genetic variation on cognitive function.

6.3.2. The contribution of environmental factors to cognitive function

This thesis provides insight into the genetic basis of cognitive dysfunction in SCZ. However, it is widely recognised in behavioural genetics that variations in cognitive function stem from the combined contributions of environmental and genetic factors (Malanchini et al., 2020; Plomin & Deary, 2015). Research indicates that environmental influences manifest through additive effects and multiplicative effects, with the latter reflecting complex gene-environment interactions (Malanchini et al., 2020; Plomin & Deary, 2015; Tucker-Drob et al., 2013). Previous studies demonstrate that the environment may mediate the effect of genetic variation on cognitive function. For example, the heritability of cognitive function is highest in high socioeconomic settings, suggesting that this environment enables children to participate in experiences that promote cognitive development based on their genetic predispositions (Tucker-Drob et al., 2013). In contrast, children from disadvantaged backgrounds are less likely to receive access to opportunities that facilitate cognitive development thus, limiting their ability to realize their genetic propensity for cognitive development (Tucker-Drob et al., 2013). Many environmental risk factors for SCZ (e.g.

obstetric complications, acute cannabis use, and childhood adversity) have been associated with cognitive impairment (McCutcheon et al., 2023). Given the contribution of environmental factors to cognitive function as well as the interaction between genes and environment in cognitive development, further work is required to elucidate the additive and multiplicative contributions of genes and the environment to cognitive function.

6.3.3. The inclusion of ancestrally diverse populations

The main genetic analyses for this thesis were conducted using data from participants of European ancestry from the UKB. In Chapter 4, the RTV-PGS showed enhanced performance in participants from the TOP study, a cohort of European ancestry, compared to participants from the SAX study, a cohort of African ancestry. These results are consistent with the poor generalizability of PGS across populations dues to differences in linkage disequilibrium, effect sizes, and allele frequencies (Majara et al., 2023). The bias in GWAS studies towards populations of European descent (Fatumo et al., 2022) has resulted in polygenic scores that are most predictive in populations of European ancestry and least predictive in African ancestry populations (Majara et al., 2023). In Chapter 5, Genomic SEM was employed to explore the factor structure of cognitive tests from the UKB. These analyses were restricted to participants of European ancestry as the method requires large sample sizes and an LD reference panel from a population that is genetically similar to the GWAS population (Grotzinger et al., 2019). As most large-scale GWAS have been conducted in populations of European descent, and because there is a scarcity of LD reference panels for non-European populations, the prerequisites for Genomic SEM generally restrict its application to European populations. ~~Similarly, most GWAS to date have been conducted in populations of European~~

~~descent as illustrated by a recent report which found that ~86% of GWAS catalogue data comes from participants of European ancestry~~

Increasing the representation of diverse global populations in genomics research is a priority to prevent the exacerbation of health inequities and advance gene discovery (Abdellaoui et al., 2023; Fatumo et al., 2022). The high levels of genetic variation observed in under-represented populations, such as African and South Asian populations, may facilitate the fine mapping of GWAS signals and the identification of likely causal genes (Atkinson et al., 2021; Fatumo et al., 2022). Thus, informing mechanistic insights which may be relevant to understanding the biological basis of disease in all populations. Finally, the poor transferability of GWAS findings across populations limits the opportunity for non-European populations to benefit from the translational aspects of genomics research (Abdellaoui et al., 2023; Majara, 2021). Given the move to integrate PRS and other findings from genomics research into clinical practice, the lack of diversity in genomics research threatens to perpetuate pre-existing treatment gaps and limit access to precision medicine for non-European populations (Abdellaoui et al., 2023; Fatumo et al., 2022).

6.3.4. Trans-diagnostic approach to investigating cognitive impairment

Cognitive impairment is not specific to schizophrenia and cognitive deficits commonly occur in other psychiatric disorders, such as bipolar disorder and major depressive disorder (Bora et al., 2013; Bora et al., 2009; Kriesche et al., 2023). It is unclear whether the pathophysiological basis of the cognitive deficits differs between psychiatric disorders (Bortolato et al., 2015). Thus, it is possible that further insight into the biological basis of cognitive impairment may be gained by adopting a transdiagnostic approach (Morris & Cuthbert, 2012). For example, studying the genetic underpinnings of WIV across different

psychiatric phenotypes, may allow for larger sample sizes and increased power for genetic discovery. Additionally, mechanistic insights derived from such analyses would not be limited to one psychiatric diagnosis and may be used to inform interventions that have the potential to benefit a larger group of mental healthcare users.

6.4. Conclusions

Overall, this thesis provides further evidence of the variable degree of impairment observed across cognitive domains in SCZ and demonstrates that this variability may be related to differences in genetic risk sharing between specific cognitive domains and SCZ. The results converge to show extensive overlap in the common genetic architecture of SCZ and cognitive function and suggest that processes related to neurodevelopment and synaptic function may be important for understanding the biological mechanisms underpinning cognitive impairment in the disorder. Further work is required to delineate these biological mechanisms and to assess the transferability of these findings to other population groups.

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Appendix 1: Supplementary Note, Figures, and Tables for Chapter 4

A. Supplementary Information

A.1. Additional cohort descriptions and methodology

This study used reaction time data from 2 independent studies for PGS analyses. The studies and operationalization of RTV in the studies are described in detail below.

The Genomics of Schizophrenia in the South African Xhosa People Study (SAX)

The SAX study is a case-control study that aimed to characterize the genetic architecture of SCZ in the Xhosa population of South Africa(Gulsuner et al., 2020). The study enrolled 2,092 individuals of African ancestry. Individuals with SCZ (cases) were recruited from inpatient psychiatric units and outpatient clinics in the Eastern Cape and Western Cape Provinces of South Africa. Controls were recruited from outpatient clinics and were matched to cases for age, gender, education and region of recruitment. Cases were individuals with a 2-year history of schizophrenia or schizoaffective disorder confirmed using the SCID-I (First & Gibbon, 2004). Informed consent was obtained from all participants and the study was approved by the University of Cape Town Human Research Ethics Committee (reference number – 049/2013).

DNA samples were obtained from participants and have been genotyped using the Affymetrix SAX v2 chip (Affymetrix Inc., Santa Clara, CA, USA). Quality control was performed using PLINK v1.9 (Chang et al., 2015) and included the removal of 1) individuals with > 5% missing data, 2) individuals with heterozygosity rate > 3 standard deviations from the mean, 3) samples with discrepancies between reported and genetically determined sex, 4) related individuals (IBD > 0.2), 5) SNPs with genotype missingness rate > 5%, 6) SNPs that deviated from Hardy-Weinberg equilibrium with p<1x10-10 in cases and p<1x10-6 in controls, 7) SNPs with a MAF

< 5%. Data was uploaded to the Wellcome Trust Sanger Institute Imputation Server (https://imputation.sanger.ac.uk/) (McCarthy et al., 2016) for phasing and imputation. Phasing was performed using EAGLE2 (Loh et al., 2016) and imputation by the Positional Burrows Wheel Transform tool (Durbin, 2014). The African Genome Resources haplotype reference panel (Abecasis et al., 2010) was used for imputation. Variants with a posterior genotype probability < 0.9 were set as missing. Post-imputation quality control included the removal of multi-allelic variants and variants with INFO score < 0.7 or MAF < 5%.

An adapted version of the University of Pennsylvania Computerized Neurocognitive Battery (PennCNB) (Gur et al., 2010) was completed by a subsample of participants. Reaction time was measured during the Penn Continuous Performance Test (PCPT) *(Kurtz et al., 2001)*. During the PCPT, participants are shown 7-segment displays at a rate of 1 per second for 3 minutes. Participants are asked to press the space bar whenever the segment forms a number during the first half of the test or a letter during the latter half. Participants are shown 180 items, 60 of which are target stimuli. Intra-individual variability in reaction time was calculated as the standard deviation in reaction time for true positive responses. RTV was log transformed to an approximately normal distribution, and the natural log of RTV was used in further analysis.

The Thematically Organised Psychosis Research Study (TOP)

The TOP study is a case-control study that recruited participants of European ancestry, born in Norway, from the Oslo region (Athanasiu et al., 2010). schizophrenia, schizoaffective, and schizophreniform disorder or bipolar disorder I, bipolar disorder II or bipolar disorder not otherwise specified (Athanasiu et al., 2010). Diagnosis was confirmed using the Structured

Clinical Interview for DSM-IV-TR-axis I disorders (First & Gibbon, 2004). Participants were considered eligible if they were aged between 18-65 years and demonstrated the ability to provide written informed consent. Individuals with pronounced cognitive deficits (IQ below 70), severe somatic illness, and brain damage were excluded from the study. Cases were recruited from psychiatric inpatient and outpatient units at major hospitals in the Oslo, Norway area as well as Trondheim, and Southeast regional hospitals in Norway (Diakonhjemmet Hospital, Lovisenberg Hospital, and St Olav's Hospital). Healthy controls were randomly selected from statistic records of individuals in the same catchment area as cases. Informed consent was provided by all participants and the human subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency.

DNA was extracted from blood and saliva samples collected at enrolment. Genotyping was performed using the Human Omni Express-24 v.1.1 (Illumina Inc., San Diego, CA, USA) at deCODE Genetics (Reykjavik, Iceland). Pre-imputation quality control was performed using PLINK 1.9 (Chang et al., 2015) and involved removal of SNPs with genotyping rate < 95%, Hardy-Weinberg disequilibrium test p-value < 10^{-4}, high rate of Mendelian errors in trios or significant (False Discovery Rate < 0.5) batch effects. Samples were excluded if they had low coverage (< 80%) or high likelihood of contamination (heterozygosity > 5 standard deviations above the mean). The quality-controlled genotypes were phased using Eagle (Loh et al., 2016), and missing variants were imputed with MaCH (Das et al., 2016; Li et al., 2010) using version 1.1 of the trans-ethnic reference sample from the Haplotype Reference Consortium (HRC) (McCarthy et al., 2016). High quality variants were selected to compute genetic principal components representing loadings along the 20 first eigenvectors of the pairwise genetic

covariance matrix of a sub-sample of unrelated individuals from the HRC panel. Following the quality control and imputation procedure, variants with information score < 0.8 or MAF < 0.01 were removed. In addition, individual genotypes imputed with < 75% confidence were set to missing, the remaining ones were converted to best guess allelic dosages.

A subsample of participants completed a battery of cognitive tests, including the continuous performance test – identical pairs (CPT-IP) version. The CPT-IP is a measure of sustained attention and during the test, participants are asked to press the mouse key as quickly as possible when two identical pairs of numbers are presented in sequence (Cornblatt et al., 1988). The CPT-IP included a 2-digit, 3-digit, and 4-digit target condition. Participants completed 150 trials for each target condition, 30% of the trials were target trials and required a response. For this study, RTV was calculated as the standard deviation in response time across trials with correct responses for the 2-digit target condition of the task.

A.2. Supplementary Methods

Phenotype Association Analyses

Association analyses were conducted between the 17 selected phenotypes and RTV using linear regression. Each trait was used as the independent variable in a linear regression with RTV as the dependent variable. Z-score standardization was applied to continuous phenotypes and the rank-based Inverse Normal Transformation was applied to RTV prior to conducting the association analysis. Age, sex, scanner site, and Euler number were included as covariates in the regression models for the 10 imaging measures. For the 7 subcortical volumes, total intracranial volume was included as an additional covariate. Age and sex were included as covariates in the association analyses for educational attainment, general

cognitive ability, neuroticism, Alzheimer's disease, ADHD, PTSD, and SCZ. Bonferroni correction for multiple testing was applied and the threshold for significance was $p < 2.94 \times 10^{-8}$.

Comparison with mean reaction time

We tested whether the genetic correlations estimates for the 17 selected traits were different for RTV compared to mean reaction time using methodology described in a previous publication (Martin et al., 2021). We calculated *z* scores for the difference in genetic correlation estimates using equation 1 (below) and obtained corresponding *p* values from a normal distribution. The Bonferroni correction was used to account for multiple testing (α = 0.05/17 traits; $p < 2.94 \times 10\text{-}3$).

$$Z - score\ difference = \frac{rg_{RTV} - rg_{Mean\ RT}}{\sqrt{SE^2_{RTV} + SE^2_{Mean\ RT}}}$$

In equation 1, rg is the genetic correlation estimate between a trait and RTV or mean reaction time obtained using linkage disequilibrium score regression; SE is the standard error of the genetic correlation estimates.

A.3. References

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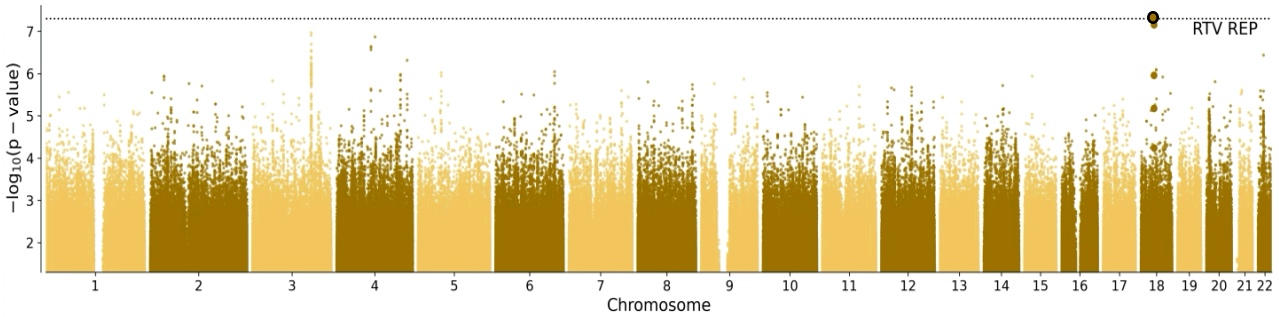
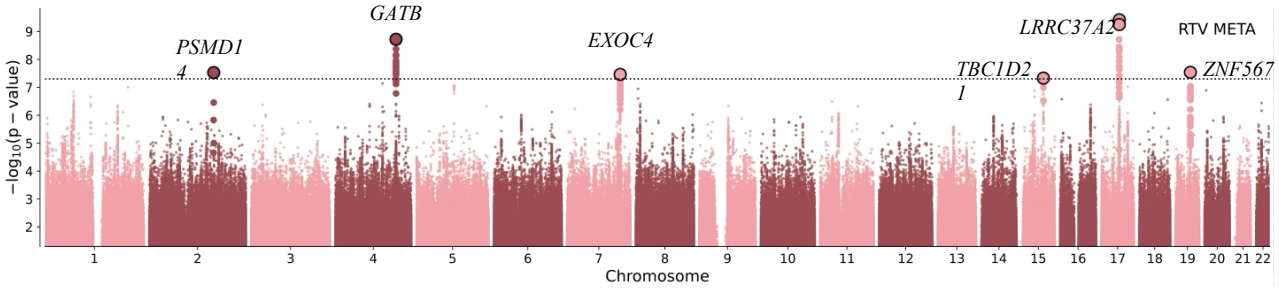
B. Supplementary Figures

A

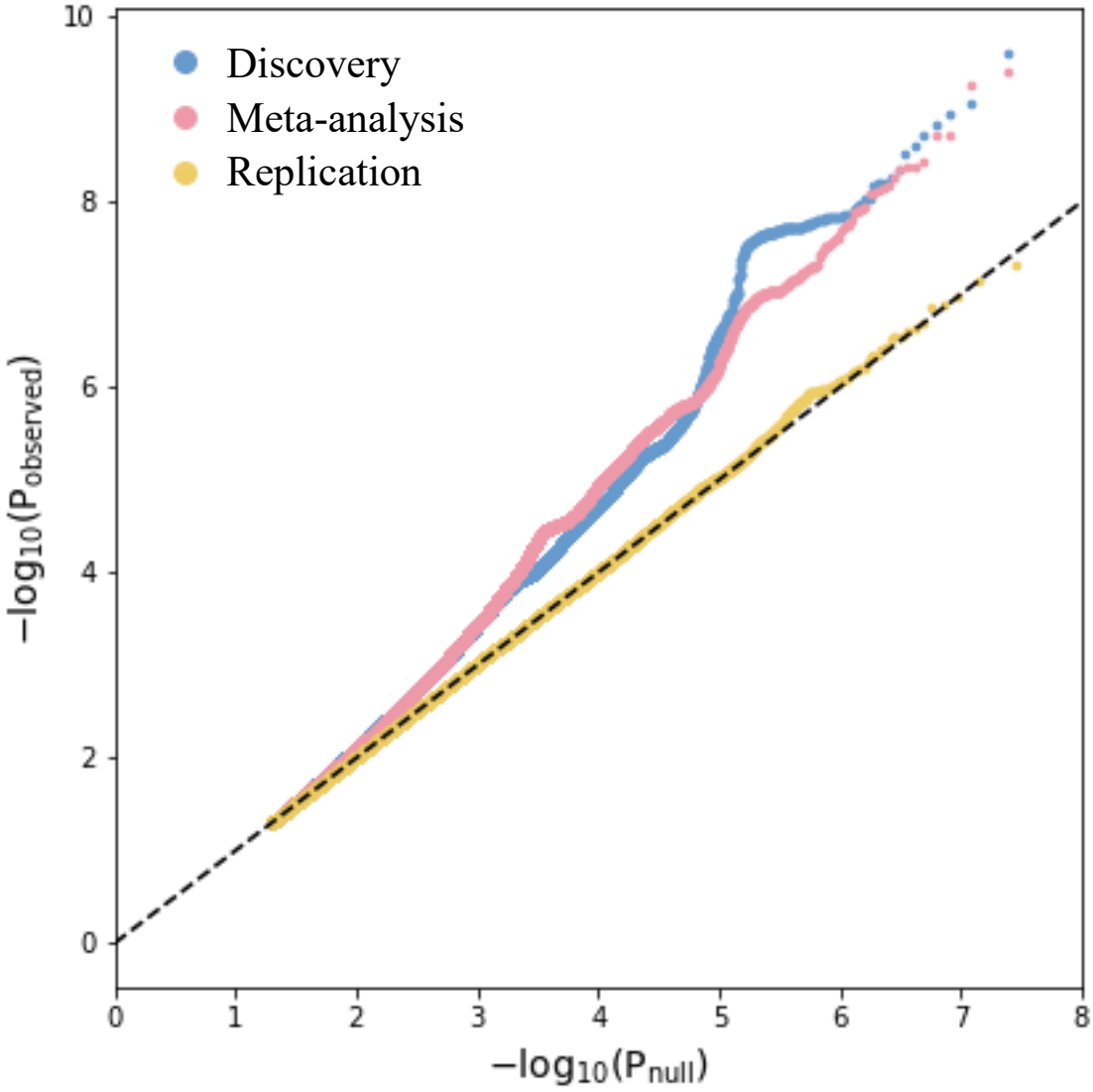


B



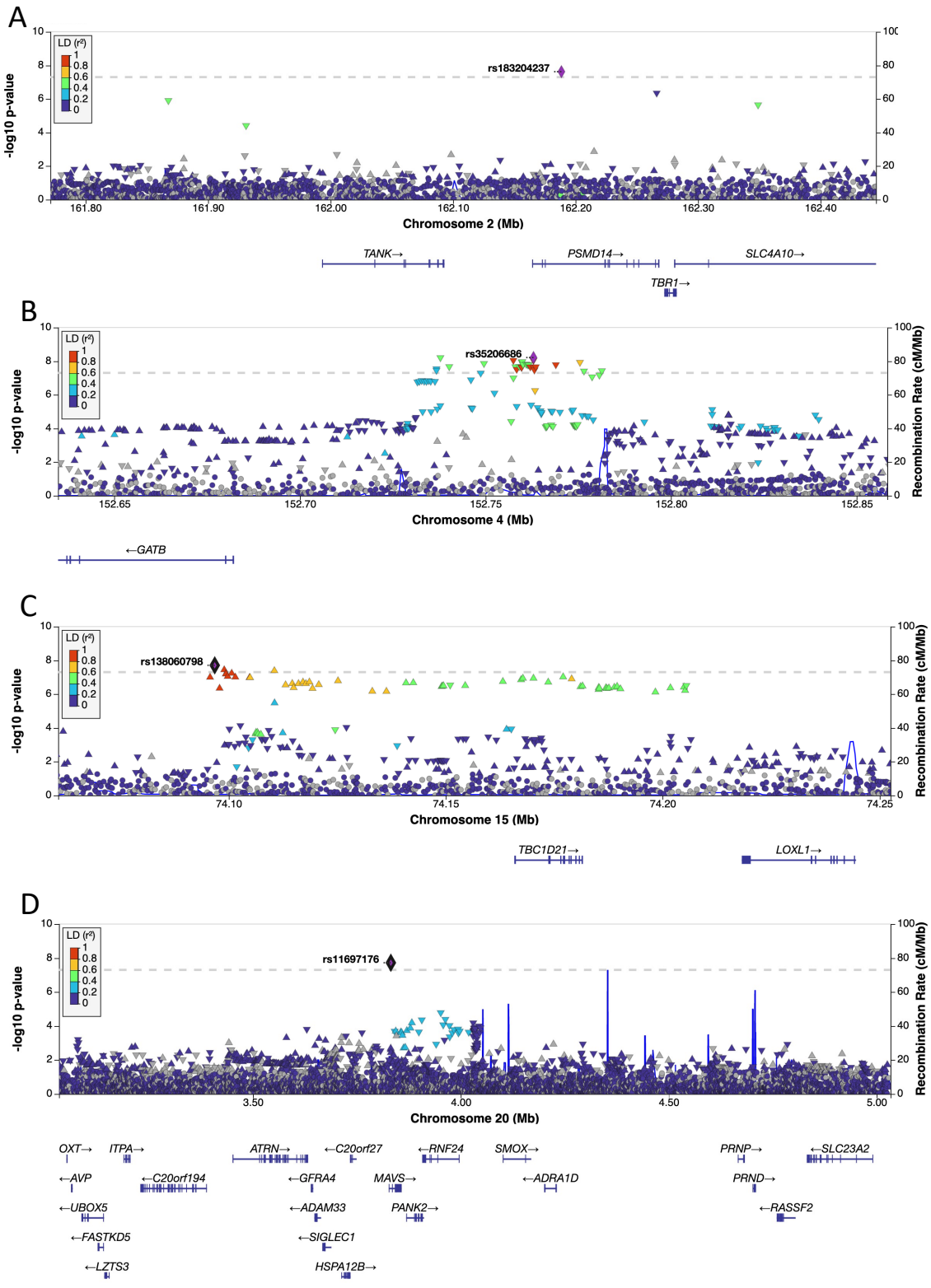
Supplementary Figure 4. 1: Manhattan Plots of the Results for the Replication GWAS (A) and Discovery and Replication GWAS Meta-analysis (B).

The Manhattan plot shows the -log10 transformed two-tailed *P*-values of SNP associations with RTV in a linear regression model against their chromosomal position. The dotted line indicates a genome-wide significance threshold of 5 x 10^{-8}. The lead SNPs from the GWAS are outlined in black and the candidate SNPs are shown in bold.



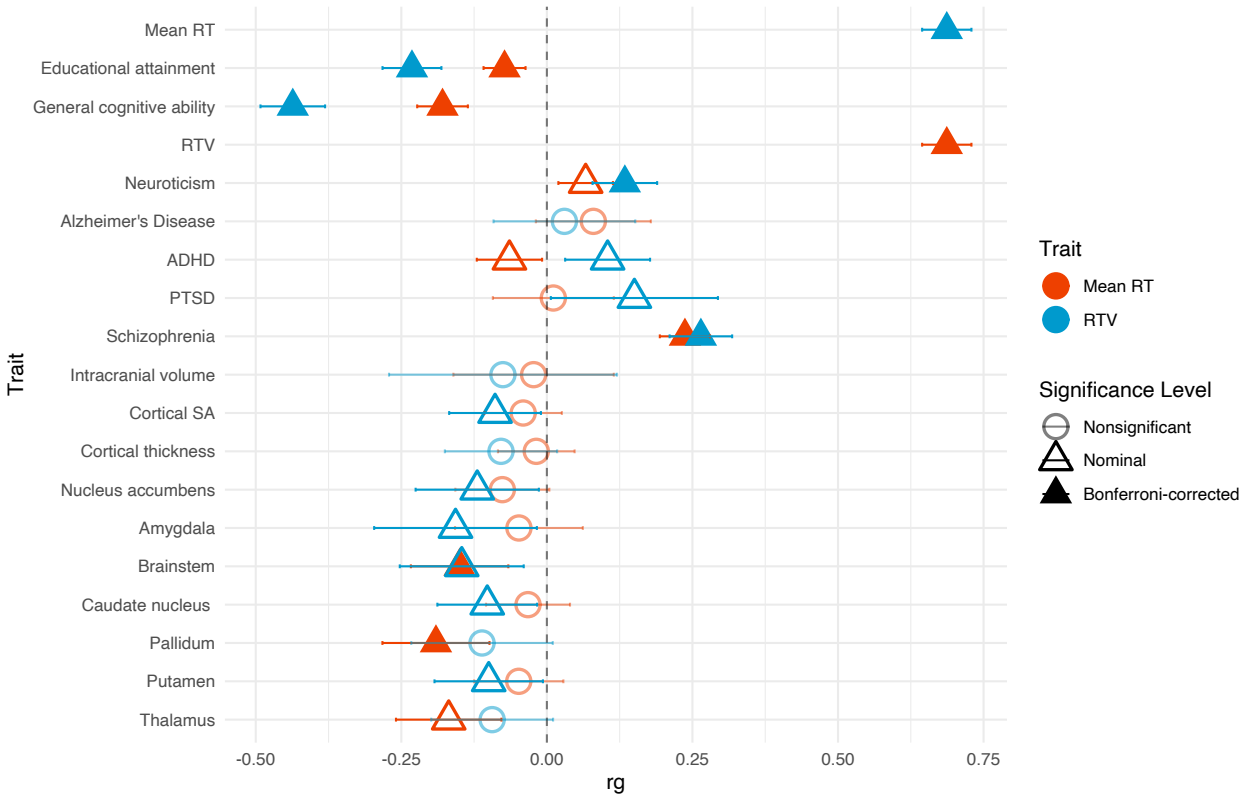
Supplementary Figure 4. 2: Quantile-quantile Plot

Quantile-quantile plot of expected under null (no association, x axis) versus observed (y axis) -$\log_{10}$ p-values for the discovery (blue), replication (pink), and discovery and replication (yellow) GWAS meta-analysis.



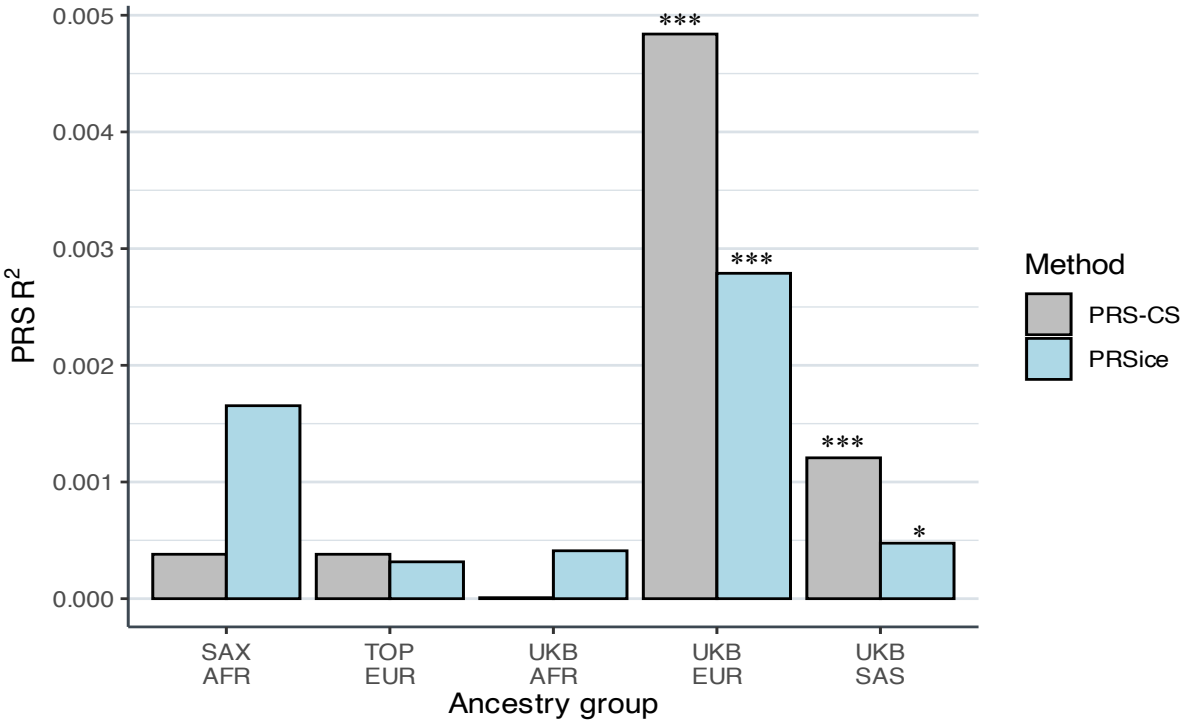
Supplementary Figure 4. 3: Regional Plots for rs183204237 (A), rs35206686 (B), rs138060798 (C), and rs11697176 (D)

The dotted line denotes a genome-wide significance threshold of 5×10^{-8}. SNPs in the genomic risk loci are colour-coded as a function of their linkage disequilibrium r^2 to the lead SNP in the region.



Supplementary Figure 4. 4: Genetic Correlations Between Mean Reaction time, RTV, and Selected traits.

Genetic correlations were calculated with LD score regression using SNP summary statistics from the Davies et al. (2018) GWAS of mean reaction time, the discovery RTV-GWAS, and publicly available summary statistics for other traits (**Supplementary Table 4.1**).



Supplementary Figure 4. 5: Prediction of RTV by Polygenic score (PGS) in Five Independent Cohorts.

The predictive accuracy of the PGS (R^2) was assessed in each cohort for a PGS calculated using two methodologies, PRSice and PRS-CS. PRSice PGS were calculated using all single nucleotide polymorphisms surviving LD pruning from the discovery GWAS (*p-value* threshold of 1).

*p<0.05, ***p<2.63 x 10^{-3}

C. Supplementary Tables

Supplementary Table 4. 1: Sample Description and Data Availability for GWAS Summary Statistics Used in Genetic Correlation Analysis

	Consortium	Data Availability	URL	N	Cohorts	Phenotyping	Reference
Educational attainment	SSGAC	Freely available	https://www.thessgac.org/data	766,345	71 cohorts. 23andMe cohort was not included in publicly available sumstats. Samples were provided from UK (largest contribution from the UKB), Estonia and USA.	The number years spent in education was calculated for all participants greater than 30 yeears old. Educational years was calculated by assigning a number of years to each educational qualification attributed to each individual based on the International Standard Classication of Education.	Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet*. 2018;50(8):1112-1121. doi:10.1038/s41588-018-0147-3
General cognitive ability	CTG	Freely available	https://ctg.cncr.nl/software/summary_statistics	269,867	14 cohorts. Largest cohort is the UKB (n=195,653).	Diverse cognitive measures were used by each cohort, the majority the measures were designed to assess fluid intelligence. Measures included: Verbal and mathematical reasoning (UKB), letter-digit substitution, Stroop, verbal fluency, delayed recall, SON-R, logical, verbal, spatial and technical ability subtests, SAT test scores, WISC-III, Raven's progressive matrices, WISC-IV, CANTAB factor score, SRT-C factor score, MAB-II IQ score, WAIS IQ score, ICAR verbal reasoning test, processing speed tests. A single cohort employed a case control design with high IQ cases compared to unselected population controls.	Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet*. 2018;50(7):912-919. doi:10.1038/s41588-018-0152-6
Mean Reaction Time		Freely available	https://www.ccace.ed.ac.uk/node/335	330,069	UK Biobank	Mean reaction time (in miliseconds) was calculated across 4 trials with matching cards for the UKB Reaction Time Test	Davies, G., Lam, M., Harris, S.E. *et al.* Study of 300,486 individuals identifies 148

						that was administered as part of the baseline assessment.	independent genetic loci influencing general cognitive function. *Nat Commun* **9**, 2098 (2018). https://doi.org/10.1038/s41467-018-04362-x
Neuroticism	CTG	Freely available	https://ctg.cncr.nl/software/summary_statistics	390,278	Meta-analysis of UKB (n=372,903) and Genetics of Personality Consortium (n=17,375). 23andMe data not included in publicly available sumstats	UKB: Summary score for neuroticism calculated by dividing the number of "Yes" answers for a 12-item questionnaire based on the Eysenck Personality Questionnaire Revised Short Form divided by the number of questions answered. <10 items answered were excluded. GPS: summay score of 12-item questionnaire using 5-point likert scales from the Big Five Inventory. Only individuals who completed all 12 items were included.	Nagel M, Jansen PR, Stringer S, et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat Genet*. 2018;50(7):920-927. doi:10.1038/s41588-018-0151-7
Alzheimer's Disease	PGC	Freely available	https://www.med.unc.edu/pgc/results-and-downloads/	86,531 cases; 676,386 controls	12 cohorts from Europe and the USA. 23andMe data not included in the publicly available summary statistics.	All samples included cases which met diagnostic criteria for Alzheimer's disease (ICD-10, NINCDS-ADRA).	Wightman, D.P., Jansen, I.E., Savage, J.E. *et al.* A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat Genet* **53**, 1276–1282 (2021). https://doi.org/10.1038/s41588-021-00921-z
ADHD	PGC	Freely available	https://www.med.unc.edu/pgc/download-results/	38,691 cases; 186,843 controls	GWAS meta-analysis of 12 cohorts (iPSYCH, deCODE genetics and 10 ADHD cohorts of European ancestry	iPSYCH: cases identified from Electronic Health Records derived from the Danish Psychiatric Central Research Register according psychiatrist attributed diagnoses using ICD10 diagnostic criteria. deCODE cases were also clinically diagnosed according to ICD10 or identified based on medication	Demontis, D., Walters, G.B., Athanasiadis, G. *et al.* Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nat*

					collected by the PGC).	prescribed specifically for ADHD. PGC Samples: Semi-structured interviews by trained researchers using (K-SADS, PACS, SDQ, MAGIC, CBCL, PICS, CAADID, CAPA, or SADDA), EHR national medical registry, or clinical diagnosis	*Genet* **55**, 198–208 (2023). https://doi.org/10.1038/s41588-022-01285-8
PTSD	PGC	Freely available	https://www.med.unc.edu/pgc/results-and-downloads/	20,329 cases; 124,440 controls	60 studies in participants of African, American and European ancestry (this work used summary statistics for GWAS in European ancestry participants)	All samples included cases which met diagnostic criteria for PTSD (DSM-III-R, DSM-IV, DSM-5, ICD-10,). Cases were defined according to clinical assessment by a psychiatrist or psychologist , structured interviews for PTSD, or self-reported PTSD.	Nievergelt, C. M., Maihofer, A. X., Klengel, T., Atkinson, E. G., Chen, C. Y., Choi, K. W., Coleman, J. R. I., Dalvie, S., Duncan, L. E., Gelernter, J., Levey, D. F., Logue, M. W., Polimanti, R., Provost, A. C., Ratanatharathorn, A., Stein, M. B., Torres, K., Aiello, A. E., Almli, L. M., Amstadter, A. B., … Koenen, K. C. (2019). International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature communications, 10(1), 4558. https://doi.org/10.1038/s41467-019-12576-w
Schizophrenia	PGC	Freely available	https://www.med.unc.edu/pgc/download-results/	53,386 cases; 77,258 controls	76 case- control samples of European descent	All samples included cases which met diagnostic criteria for either schizophrenia or schizoaffective disorder (DSM-III, DSM-IV, DSM-V, ICD-10,). Cases were defined according to clinical assessment by a psychiatrist or psychologist , structured interviews (SCID, SCAN, SADS-L, DiPAD, SHIP,	Trubetskoy, V., Pardiñas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., Bryois, J., Chen, C. Y., Dennison, C. A., Hall, L. S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J. C., Koopmans, F.,

						PANSS, DIGS, FIGS, BEFD), and expert review of EHRs.	Magnusson, S., Richards, A. L., Sidorenko, J., Wu, Y., … Schizophrenia Working Group of the Psychiatric Genomics Consortium (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, *6 04*(7906), 502–508. https://doi.org/10.1038/s41586-022-04434-5
Intracranial volume	ENIGMA	Available on request	https://enigma.ini.usc.edu/research/download-enigma-gwas-results/	9,826	50 contributing sites. Summary statistics used exclude overlapping particpants with the PGC schizophrenia 2014 GWAS.	Structural MRI data was collected,processed and examined at each participating site locally, following a standardized protocol procedure to harmonize the analysis across sites.	Hibar, D., Stein, J., Renteria, M. *et al.* Common genetic variants influence human subcortical brain structures. *Nature* **520**, 224–229 (2015). https://doi.org/10.1038/nature14101
Cortical surface area	ENIGMA	Available on request	https://enigma.ini.usc.edu/research/download-enigma-gwas-results/	33,992	60 contributing sites. Predominantly European ancestry.	Measures of cortical surface area and thickness were derived from in vivo whole-brain T1-weighted MRI scans using FreeSurfer MRI-processing software . Cortical surface area and thickness were quantified for each individual across the whole cortex and within 34 distinct gyral-defined regions, according to the Desikan-Killiany atlas.	Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., Lind, P. A., Pizzagalli, F., Ching, C. R. K., McMahon, M. A. B., Shatokhina, N., Zsembik, L. C. P., Thomopoulos, S. I., Zhu, A. H., Strike, L. T., Agartz, I., Alhusaini, S., Almeida, M. A. A., Alnæs, D., Amlien, I. K., … Enhancing NeuroImaging Genetics through Meta-Analysis

							Consortium (ENIGMA)—Genetics working group (2020). The genetic architecture of the human cerebral cortex. *Science (New York, N.Y.)*, *367*(6484), eaay6690. https://doi.org/10.1126/science.aay6690
Cortical thickness	ENIGMA	Available on request	https://enigma.ini.usc.edu/research/download-enigma-gwas-results/	33,992	60 contributing sites. Predominantly European ancestry.	Measures of cortical surface area and thickness were derived from in vivo whole-brain T1-weighted MRI scans using FreeSurfer MRI-processing software . Cortical surface area and thickness were quantified for each individual across the whole cortex and within 34 distinct gyral-defined regions, according to the Desikan-Killiany atlas.	Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., Lind, P. A., Pizzagalli, F., Ching, C. R. K., McMahon, M. A. B., Shatokhina, N., Zsembik, L. C. P., Thomopoulos, S. I., Zhu, A. H., Strike, L. T., Agartz, I., Alhusaini, S., Almeida, M. A. A., Alnæs, D., Amlien, I. K., … Enhancing NeuroImaging Genetics through Meta-Analysis Consortium (ENIGMA)—Genetics working group (2020). The genetic architecture of the human cerebral cortex. *Science (New York, N.Y.)*, *367*(6484), eaay6690. https://doi.org/10.1126/science.aay6690

Nucleus accumbens	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	32,562	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed and examined at each site locally. Subcortical brain measures were delineated in the brain using well-validated, freely available brain segmentation software packages. The volume of the subcortical structure was defined as the mean volume (in cm^3) of the left and right hemispheres.	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636 (2019). https://doi.org/10.1038/s41588-019-0511-y
Amygdala	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	34,431	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed and examined at each site locally. Subcortical brain measures were delineated in the brain using well-validated, freely available brain segmentation software packages. The volume of the subcortical structure was defined as the mean volume (in cm^3) of the left and right hemispheres.	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636 (2019). https://doi.org/10.1038/s41588-019-0511-y
Brainstem	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	28,809	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed at examined at each site locally, following a standardized protocol procedure to harmonize the analysis across sites. Subcortical brain measures were delineated in the brain using well-validated, freely available brain segmentation software packages. The volume of the brainstem was defined as the total volume (in cm^3).	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636 (2019). https://doi.org/10.1038/s41588-019-0511-y

Caudate Nucleus	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	37,741	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed and examined at each site locally. Subcortical brain measures were delineated in the brain using well-validated, freely available brain segmentation software packages. The volume of the subcortical structure was defined as the mean volume (in cm^3) of the left and right hemispheres.	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636 (2019). https://doi.org/10.1038/s41588-019-0511-y
Pallidum	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	34,413	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed and examined at each site locally. Subcortical brain measures were delineated in the brain using well-validated, freely available brain segmentation software packages. The volume of the subcortical structure was defined as the mean volume (in cm^3) of the left and right hemispheres.	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636 (2019). https://doi.org/10.1038/s41588-019-0511-y
Putamen	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	37,571	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed and examined at each site locally. Subcortical brain measures were delineated in the brain using well-validated, freely available brain segmentation software packages. The volume of the subcortical structure was defined as the mean volume (in cm^3) of the left and right hemispheres.	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636 (2019). https://doi.org/10.1038/s41588-019-0511-y
Thalamus	CHARGE, ENIGMA & UKB	Available on request from the CHARGE dbGaP and ENIGMA websites	http://enigma.ini.usc.edu/research/download-enigma-gwas-results	34,464	48 contributing studies across the 3 cohorts. Summary statistics for GWAS in European ancestry group.	Structural MRI data collected at participating sites. Brain scans were processed and examined at each site locally. Subcortical brain measures were delineated in the brain using well-validated, freely available brain	Satizabal, C.L., Adams, H.H.H., Hibar, D.P. *et al.* Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat Genet* **51**, 1624–1636

						segmentation software packages. The volume of the subcortical structure was defined as the mean volume (in cm^3) of the left and right hemispheres.	(2019). https://doi.org/10.1038/s41588-019-0511-y

Supplementary Table 4. 2: Description of Additional UK Biobank Phenotypes Used for Regression Analysis

Trait	N	Data Field	Definition
Educational attainment	490,461	6138	Ordinal variable asessing highest level of education at baseline.
General cognitive ability	163,883	20016	The UKB Fluid IQ is a test of verbal and numerical reasoning. The participants are given a 2 minute time limit to answer 13 multiple-choice questions. The score is taken as the number of correct answers. Fluid intellligence scores from the baseline assessment were used for this analysis.
Neuroticism	401,483	20127	Summary score for neurotic behaviour calculated from a 12-item 12-item questionnaire based on the Eysenck Personality Questionnaire Revised Short Form.
Alzheimer's Disease	2,350 cases	41270	Any primary or secondary diagnosis of Alzheimer's Disease according to all hospital in-patient records. Diagnosis coded according to the ICD-10. Diagnostic code: F00. Sample includes 2,350 participants with a diagnosis of Alzheimer's Disease.
ADHD	133 cases	20544	Question assessing whether participants have ever been diagnosed with 1 of 16 mental health disorders by a healthcare professional. 133 participants reported a diagnosis of ADHD.
PTSD	526 cases	41270	Any primary or secondary diagnosis of PTSD according to all hospital in-patient records. Diagnosis coded according to the ICD-10. Diagnostic code: F43.1. Sample includes 526 participants with a diagnosis of Alzheimer's Disease.
Schizophrenia	1,199 cases	130874, 130875	Date and source of first reported diagnosis of schizophrenia. Diagnosis coded according to the ICD-10. Diagnostic code: F20. Sample includes 1,199 people with a diagnosis of schizophrenia.
Intracranial volume	41,276		T1 weighted scans were collected from 4 scanning sites using identically configured Siemens MAGNETOM Skyra 3T scanners (Simens AG). Images were processed using the standard FreeSurfer recon-all pipeline (v5.3, http://surfer.nmr.mgh.harvard.edu). The volume of the subcortical structure was defined as the mean volume of the left and right hemispheres, with the exception of the braintem for which the total volume was used. Cortical thickness was averaged across both hemispheres. Cortical surface area was measured at the grey-white matter boundary and total surface area was calculated across both hemispheres.
Cortical surface area	41,276		
Cortical thickness	41,276		
Nucleus accumbens	41,276		
Amygdala	41,276		
Brainstem	41,276		
Caudate Nucleus	41,276		
Pallidum	41,276		
Putamen	41,276		
Thalamus	41,276		

Supplementary Table 4. 3: Summary Statistics and Functional Annotation for SNPs Reaching Genome-wide Significance in Discovery GWAS

Note: The effect size (BETA) and standard error (SE) are given for the effect allele (A1) in the discovery GWAS of RTV in 404,302 inidividuals, Independent (r2 < ,1) lead snps in a region are in red, MAF = minor allele frequency based on the 1000 Genomes Project Phase 3 release European reference panel, ANNOVAR = functional variant classification based on position in or outside of a gene; CADD = Combined Annotation-Dependent depletion score, ; RDB = RegulomeDB scores; minChrState = minimum chromatin state across 127 tissue types ; commonChrState = most common chromatin state in 127 tissue types.

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs183204237	2	162188514	G	C	0.003	2.38E-08	-0.210	0.038	1.000	rs183204237	1	PSMD14	0	intronic	3.47	5	4	5
rs55764665	4	152736789	G	A	0.371	2.85E-08	-0.013	0.002	1.000	rs55764665	2	RP11-424M21.1	14288	intergenic	2.67	7	5	15
rs56237622	4	152736791	T	G	0.373	3.54E-08	-0.013	0.002	0.992	rs55764665	2	RP11-424M21.1	14290	intergenic	1.04	7	5	15
rs7684366	4	152737856	T	C	0.239	6.20E-09	-0.015	0.003	1.000	rs7684366	2	RP11-424M21.1	15355	intergenic	1.47	6	5	15
rs2136959	4	152740233	A	G	0.247	2.12E-08	-0.015	0.003	0.957	rs7684366	2	RP11-424M21.1	17732	intergenic	0.51	7	9	15
rs1385253	4	152749595	T	C	0.242	1.38E-08	-0.015	0.003	0.984	rs7684366	2	RP11-424M21.1	27094	intergenic	0.71	7	14	15
rs361199	4	152757511	A	T	0.289	8.97E-09	-0.015	0.003	0.916	rs35206686	2	RP11-424M21.1	35010	intergenic	0.57	6	5	15
rs361200	4	152758061	A	T	0.389	2.16E-08	-0.013	0.002	0.996	rs361206	2	RP11-424M21.1	35560	intergenic	2.06	7	5	15
rs361202	4	152758408	T	C	0.286	3.09E-08	-0.014	0.003	0.940	rs35206686	2	RP11-424M21.1	35907	intergenic	9.31	7	5	15
rs181731	4	152759119	T	C	0.389	2.07E-08	-0.013	0.002	0.996	rs361206	2	RP11-424M21.1	36618	intergenic	0.21	7	5	15
rs361203	4	152759653	T	A	0.287	2.22E-08	-0.014	0.003	0.944	rs35206686	2	RP11-424M21.1	37152	intergenic	0.05	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs361204	4	152759741	T	G	0.287	2.36E-08	-0.014	0.003	0.944	rs35206686	2	RP11-424M21.1	37240	intergenic	1.24	7	5	15
rs361205	4	152759751	C	T	0.390	1.12E-08	-0.013	0.002	1.000	rs361206	2	RP11-424M21.1	37250	intergenic	0.5	6	5	15
rs361206	4	152759925	C	A	0.390	1.08E-08	-0.013	0.002	1.000	rs361206	2	RP11-424M21.1	37424	intergenic	0.14	6	5	15
rs361207	4	152760129	A	G	0.390	1.60E-08	-0.013	0.002	1.000	rs361206	2	RP11-424M21.1	37628	intergenic	0.93	7	5	15
rs10000280	4	152760983	G	C	0.390	1.51E-08	-0.013	0.002	1.000	rs361206	2	RP11-424M21.1	38482	intergenic	0.26	7	5	15
rs191716	4	152761365	C	T	0.390	1.61E-08	-0.013	0.002	1.000	rs361206	2	RP11-424M21.1	38864	intergenic	2.88	6	5	15
rs361191	4	152761633	T	G	0.388	1.65E-08	-0.013	0.002	0.992	rs361206	2	RP11-424M21.1	39132	intergenic	4.54	6	5	15
rs361192	4	152762072	G	C	0.287	2.18E-08	-0.014	0.003	0.944	rs35206686	2	RP11-424M21.1	39571	intergenic	10.2	7	5	15
rs361194	4	152762925	G	T	0.293	8.98E-09	-0.014	0.003	0.972	rs35206686	2	RP11-424M21.1	40424	intergenic	1.1	NA	5	15
rs35206686	4	152762934	TC	T	0.299	6.09E-09	-0.015	0.003	1.000	rs35206686	2	RP11-424M21.1	40433	intergenic	1.72	NA	5	15
rs361195	4	152763021	C	G	0.287	2.49E-08	-0.014	0.003	0.944	rs35206686	2	RP11-424M21.1	40520	intergenic	1.24	6	5	15
rs361196	4	152763180	T	C	0.287	3.39E-08	-0.014	0.003	0.944	rs35206686	2	RP11-424M21.1	40679	intergenic	5.68	5	5	15
rs361197	4	152763556	A	G	0.287	2.16E-08	-0.014	0.003	0.944	rs35206686	2	RP11-424M21.1	41055	intergenic	3.91	5	5	15
rs361212	4	152768951	T	C	0.283	1.63E-08	-0.014	0.003	0.908	rs35206686	2	RP11-503L23.1	39743	intergenic	1.89	7	5	15
rs189679	4	152775454	C	G	0.222	1.18E-08	-0.015	0.003	0.681	rs528612	2	RP11-503L23.1	33240	intergenic	0.59	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs361209	4	152776538	G	A	0.303	3.88E-08	-0.014	0.002	0.911	rs528612	2	RP11-503L23.1	32156	intergenic	2.28	6	5	15
rs528612	4	152781361	T	C	0.287	3.74E-08	-0.014	0.003	1.000	rs528612	2	RP11-503L23.1	27333	intergenic	0.89	6	5	15
rs2345941	7	133337635	A	G	0.452	2.50E-08	0.012	0.002	0.905	rs17167210	3	EXOC4	0	intronic	2.07	5	5	15
rs2066924	7	133338462	C	A	0.448	2.31E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	2.66	NA	5	15
rs17167210	7	133339343	G	A	0.431	1.50E-09	0.013	0.002	1.000	rs17167210	3	EXOC4	0	intronic	1.22	5	5	15
rs2483507	7	133339546	C	T	0.448	2.36E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	2.78	5	5	15
rs2483509	7	133341162	G	A	0.451	1.63E-08	0.012	0.002	0.924	rs17167210	3	EXOC4	0	intronic	0.9	6	5	15
rs12530581	7	133342955	A	T	0.448	2.36E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.31	7	5	15
rs763643	7	133343243	T	A	0.448	2.37E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	6.27	5	5	15
rs763644	7	133343349	G	C	0.448	2.31E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.84	5	5	15
rs763646	7	133343353	C	T	0.448	3.31E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	3.23	5	5	15
rs763645	7	133343428	C	T	0.448	2.47E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.67	7	5	15
rs6970448	7	133343642	G	A	0.448	2.55E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.8	6	5	15
rs4731974	7	133344010	C	T	0.448	2.55E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	2.69	6	5	15
rs4728296	7	133344566	C	T	0.448	2.68E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.2	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs7776986	7	133345635	C	T	0.449	2.25E-08	-0.012	0.002	0.931	rs17167210	3	EXOC4	0	intronic	9.95	5	5	15
rs10236819	7	133345983	A	T	0.448	2.58E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.86	7	5	15
rs10266435	7	133346081	C	T	0.448	2.95E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	0.45	7	5	15
rs1133540	7	133346380	C	T	0.448	2.61E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	1.32	7	5	15
rs17601462	7	133347066	A	G	0.448	3.09E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	7.76	7	5	15
rs10231828	7	133348337	T	G	0.450	2.21E-08	0.012	0.002	0.927	rs17167210	3	EXOC4	0	intronic	2.59	6	4	15
rs10231829	7	133348338	T	A	0.450	2.20E-08	0.012	0.002	0.927	rs17167210	3	EXOC4	0	intronic	1.26	6	4	15
rs2430769	7	133349149	G	A	0.449	1.89E-08	0.012	0.002	0.931	rs17167210	3	EXOC4	0	intronic	4.69	5	5	15
rs1014442	7	133349281	A	T	0.448	2.38E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	1.19	5	5	15
rs10808271	7	133352318	T	C	0.448	2.86E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	4.05	5	5	15
rs1041621	7	133353965	G	A	0.448	2.59E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	2.09	NA	5	15
rs17659708	7	133355098	A	G	0.448	2.58E-08	0.012	0.002	0.934	rs17167210	3	EXOC4	0	intronic	1.09	4	5	15
rs62471409	7	133371246	C	T	0.430	1.59E-08	0.012	0.002	0.848	rs17167210	3	EXOC4	0	intronic	0.27	7	5	15
rs1833334	7	133371836	C	T	0.430	1.77E-08	0.012	0.002	0.848	rs17167210	3	EXOC4	0	intronic	0.38	7	5	15
rs2041996	7	133390510	G	A	0.429	2.98E-08	0.012	0.002	0.844	rs17167210	3	EXOC4	0	intronic	2.73	4	2	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs2016876	7	133395492	T	G	0.429	2.58E-08	0.012	0.002	0.844	rs17167210	3	EXOC4	0	intronic	5.81	5	5	15
rs12707117	7	133429058	G	A	0.432	2.12E-08	-0.012	0.002	0.841	rs17167210	3	EXOC4	0	intronic	0	7	5	15
rs11768260	7	133430482	T	C	0.424	4.82E-08	0.012	0.002	0.820	rs17167210	3	EXOC4	0	intronic	0.9	6	5	15
rs10954431	7	133430901	G	T	0.429	1.51E-08	0.012	0.002	0.844	rs17167210	3	EXOC4	0	intronic	1.5	7	5	15
rs10247014	7	133431038	G	T	0.430	1.74E-08	0.012	0.002	0.848	rs17167210	3	EXOC4	0	intronic	2.2	6	5	15
rs9649046	7	133433402	G	A	0.429	1.59E-08	0.012	0.002	0.844	rs17167210	3	EXOC4	0	intronic	2.05	4	5	15
rs2551023	7	133472662	A	C	0.456	2.57E-08	0.012	0.002	0.757	rs17167210	3	EXOC4	0	intronic	2.82	NA	5	15
rs2113336	7	133478107	C	A	0.453	2.23E-08	0.012	0.002	0.760	rs17167210	3	EXOC4	0	intronic	0.86	NA	5	15
rs2542274	7	133491069	C	T	0.453	3.19E-08	0.012	0.002	0.760	rs17167210	3	EXOC4	0	intronic	2.21	7	5	15
rs2550986	7	133501113	G	A	0.454	2.49E-08	0.012	0.002	0.759	rs55812659	3	EXOC4	0	intronic	2.42	NA	5	15
rs34678688	7	133504607	A	AC	0.454	2.22E-08	-0.012	0.002	0.759	rs55812659	3	EXOC4	0	intronic	3.23	NA	4	5
rs7786100	7	133505716	G	T	0.457	4.25E-08	-0.012	0.002	0.753	rs17167210	3	EXOC4	0	intronic	1.59	5	4	5
rs6944452	7	133522387	A	G	0.454	2.14E-08	-0.012	0.002	0.750	rs17167210	3	EXOC4	0	intronic	1.95	3a	5	15
rs7802352	7	133523259	T	C	0.451	2.78E-08	-0.012	0.002	0.753	rs17167210	3	EXOC4	0	intronic	1.5	7	5	15
7:133532290_ATT_A	7	133532290	ATT	A	0.497	1.35E-08	-0.013	0.002	0.649	rs17167210	3	EXOC4	0	intronic	0.12	NA	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs6972284	7	133535714	T	C	0.453	4.85E-08	-0.012	0.002	0.760	rs17167210	3	EXOC4	0	intronic	8.66	5	5	15
rs6954207	7	133560955	C	T	0.459	2.89E-08	-0.012	0.002	0.756	rs55812659	3	EXOC4	0	intronic	6.54	5	5	15
rs6954859	7	133561464	A	G	0.454	2.86E-08	-0.012	0.002	0.761	rs55812659	3	EXOC4	0	intronic	1.81	5	5	15
rs12707124	7	133566423	T	C	0.455	2.03E-08	-0.012	0.002	0.763	rs55812659	3	EXOC4	0	intronic	4.5	5	5	15
rs10156038	7	133570725	T	A	0.458	1.69E-08	-0.012	0.002	0.754	rs55812659	3	EXOC4	0	intronic	1.36	5	5	15
rs12707125	7	133570858	A	G	0.457	1.93E-08	-0.012	0.002	0.760	rs55812659	3	EXOC4	0	intronic	3.18	5	5	15
rs6967343	7	133571797	A	G	0.454	1.45E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	7.41	5	5	15
rs6467506	7	133572410	A	G	0.454	1.74E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	8.53	4	5	15
rs56255935	7	133572945	T	TCCC	0.457	2.92E-08	-0.012	0.002	0.760	rs55812659	3	EXOC4	0	intronic	2.13	NA	5	15
rs10246164	7	133573039	T	C	0.457	1.85E-08	-0.012	0.002	0.760	rs55812659	3	EXOC4	0	intronic	14.3	5	5	15
rs10246406	7	133573222	T	A	0.457	1.86E-08	-0.012	0.002	0.760	rs55812659	3	EXOC4	0	intronic	9.75	4	5	15
rs10231158	7	133573540	C	G	0.457	2.12E-08	-0.012	0.002	0.760	rs55812659	3	EXOC4	0	intronic	5.31	5	5	15
rs6978533	7	133574051	A	C	0.454	1.81E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.66	7	5	15
rs201882079	7	133577600	T	A	0.458	3.05E-08	-0.012	0.002	0.753	rs55812659	3	EXOC4	0	intronic	3.62	7	5	15
rs199741058	7	133578800	G	A	0.451	3.88E-08	-0.012	0.002	0.756	rs55812659	3	EXOC4	0	intronic	2.56	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs201376358	7	133579006	T	C	0.460	4.03E-08	-0.012	0.002	0.750	rs55812659	3	EXOC4	0	intronic	4.07	7	5	15
rs7788061	7	133579844	T	C	0.458	2.12E-08	-0.012	0.002	0.763	rs55812659	3	EXOC4	0	intronic	3.61	7	5	5
rs7805268	7	133579980	G	A	0.455	2.47E-08	-0.012	0.002	0.765	rs55812659	3	EXOC4	0	intronic	3.27	6	5	5
rs2042454	7	133580710	A	G	0.454	2.04E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	5.21	NA	4	5
rs2042452	7	133581093	A	G	0.454	2.24E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	11	NA	4	5
rs2288067	7	133581102	A	G	0.454	2.09E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	13.8	NA	4	5
7:133581274_AG_A	7	133581274	AG	A	0.455	2.48E-08	-0.012	0.002	0.771	rs55812659	3	EXOC4	0	intronic	0.31	NA	4	5
rs6467507	7	133581480	A	G	0.455	1.40E-08	-0.013	0.002	0.765	rs55812659	3	EXOC4	0	intronic	0.44	7	4	5
rs7794229	7	133581563	T	C	0.454	2.56E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	0.47	6	4	5
rs13309851	7	133582364	C	A	0.457	1.48E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	0.45	5	4	5
rs777716181	7	133582502	CT	C	0.457	1.45E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	0.67	NA	5	5
rs7793582	7	133582851	G	A	0.457	1.43E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	2.86	6	5	5
rs7793732	7	133582953	G	T	0.457	1.43E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	0.75	7	5	5
rs7793739	7	133582973	G	T	0.457	1.41E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	2.48	7	5	5
rs7776858	7	133583144	T	C	0.457	1.44E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	2.56	6	5	5

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs7793959	7	133583280	C	T	0.457	2.06E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	3.61	6	5	5
rs112523920	7	133583296	A	AGACCATCCTG	0.455	1.91E-08	-0.012	0.002	0.771	rs55812659	3	EXOC4	0	intronic	0.88	NA	5	5
rs13312097	7	133583603	T	C	0.457	1.48E-08	-0.012	0.002	0.757	rs55812659	3	EXOC4	0	intronic	0.11	7	5	15
rs7798192	7	133583841	A	T	0.454	1.93E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	0.97	5	5	15
rs7798355	7	133583899	A	G	0.454	1.93E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	5.72	5	5	15
rs7798673	7	133584077	C	T	0.454	1.91E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.12	4	5	15
rs12707126	7	133584271	A	G	0.454	2.97E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.42	5	5	15
rs6971638	7	133585386	A	G	0.454	1.92E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	7.85	7	5	15
rs6971840	7	133585570	A	G	0.454	1.89E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	7.28	6	5	15
rs6954537	7	133585612	T	C	0.454	1.79E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	5.96	6	5	15
rs6972423	7	133585678	G	A	0.454	1.89E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.77	7	5	15
rs6976416	7	133585752	G	A	0.454	1.84E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.15	7	5	15
rs6976885	7	133585989	G	A	0.453	1.93E-08	-0.012	0.002	0.766	rs55812659	3	EXOC4	0	intronic	13.9	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs12707127	7	133586089	A	G	0.454	1.89E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	3.87	7	5	15
rs7782545	7	133587689	C	T	0.454	2.02E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.66	7	5	15
rs7783179	7	133588117	C	G	0.454	2.03E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.03	7	5	15
rs10241782	7	133588380	A	G	0.455	1.97E-08	-0.012	0.002	0.765	rs55812659	3	EXOC4	0	intronic	4.04	5	5	15
rs10271671	7	133588413	G	A	0.455	1.99E-08	-0.012	0.002	0.765	rs55812659	3	EXOC4	0	intronic	6.54	5	5	15
rs6950081	7	133588565	A	G	0.454	1.90E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	0.37	7	5	15
rs6974386	7	133588738	T	C	0.454	1.90E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	6.4	6	4	15
rs6954999	7	133588927	G	A	0.454	1.85E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	3.51	7	4	15
rs6955061	7	133589145	C	T	0.454	1.92E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	4.22	7	4	15
rs6975860	7	133589584	T	G	0.454	1.88E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	15.5	5	4	15
rs6956135	7	133589608	G	T	0.454	1.90E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	13.9	5	4	15
rs1862873	7	133590287	T	A	0.455	2.23E-08	-0.012	0.002	0.765	rs55812659	3	EXOC4	0	intronic	0.77	7	4	15
rs2113339	7	133591473	A	G	0.454	2.88E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	3.47	NA	4	15
rs2113338	7	133591539	T	C	0.454	2.38E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.99	NA	4	15
rs2042451	7	133593030	A	G	0.454	2.26E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.65	6	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs1593171	7	133597442	G	C	0.454	2.40E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	3.78	7	1	15
rs5887650	7	133602902	A	AT	0.454	2.14E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.53	NA	4	5
rs1862872	7	133602934	A	C	0.454	2.01E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.52	NA	4	5
rs751967768	7	133603493	TA	T	0.454	2.05E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	2.14	NA	4	5
rs4422723	7	133606158	A	T	0.454	2.76E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	5.57	7	4	8
rs4517044	7	133607014	T	A	0.454	2.56E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.32	5	5	15
rs1963841	7	133607535	A	G	0.454	2.77E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	1.98	NA	5	15
7:133607740_GT_G	7	133607740	GT	G	0.455	1.67E-08	-0.012	0.002	0.763	rs55812659	3	EXOC4	0	intronic	0.51	NA	5	15
rs55812659	7	133608748	G	GT	0.479	1.08E-08	-0.013	0.002	1.000	rs55812659	3	EXOC4	0	intronic	0.4	NA	5	15
rs10263851	7	133611256	C	T	0.454	2.83E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	0.63	6	5	15
7:133614230_GA_G	7	133614230	GA	G	0.452	2.28E-08	-0.012	0.002	0.752	rs55812659	3	EXOC4	0	intronic	1.9	NA	5	15
rs6970436	7	133614710	A	G	0.454	2.47E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	0.98	7	5	15
rs1025074	7	133615559	G	A	0.453	1.91E-08	-0.012	0.002	0.765	rs55812659	3	EXOC4	0	intronic	0.86	NA	5	15
7:133617799_AT_A	7	133617799	AT	A	0.442	1.49E-08	-0.013	0.002	0.704	rs55812659	3	EXOC4	0	intronic	0.58	NA	4	15
rs6954610	7	133618986	A	G	0.454	2.24E-08	-0.012	0.002	0.769	rs55812659	3	EXOC4	0	intronic	12.6	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs35859241	15	51736660	A	G	0.221	3.69E-08	-0.014	0.003	1.000	rs35859241	4	RP11-707P17.1	0	ncRNA_intronic	0.52	7	5	15
rs912243472	15	74096786	GA	G	0.146	1.97E-08	0.018	0.003	1.000	rs912243472	5	RP11-8P11.3	34807	intergenic	2.11	NA	5	15
rs10656461	15	74098972	G	GAGA	0.141	3.64E-08	0.018	0.003	0.964	15:74096786_GA_G	5	RP11-8P11.3	36993	intergenic	4.53	NA	2	15
rs72743368	15	74110523	C	T	0.116	4.12E-08	0.019	0.003	0.763	15:74096786_GA_G	5	RP11-8P11.3	48544	intergenic	2.38	4	6	15
rs7209589	17	44369420	A	G	0.247	1.15E-09	0.017	0.003	0.877	rs1863115	6	ARL17B	0	intronic	0.8	7	5	15
rs536912361	17	44382820	A	G	0.209	1.96E-08	-0.017	0.003	0.699	rs1863115	6	ARL17B:LRRC37A	00:00	intronic	0.8	NA	15	15
rs273534	17	44410179	T	C	0.251	1.91E-09	0.017	0.003	0.879	rs1863115	6	ARL17B:LRRC37A	00:00	intronic	1.77	6	5	15
rs2137113	17	44410368	T	G	0.246	4.51E-09	0.016	0.003	0.890	rs1863115	6	ARL17B:LRRC37A	00:00	intronic	13.2	6	5	15
rs144216645	17	44623789	T	C	0.271	1.74E-08	0.015	0.003	0.837	rs1863115	6	LRRC37A2:ARL17A	00:00	intronic	9.9	6	5	15
rs1863115	17	44625928	C	A	0.252	2.47E-10	0.017	0.003	1.000	rs1863115	6	LRRC37A2:ARL17A	00:00	exonic	18.3	6	5	15
rs147382204	17	44768597	T	G	0.334	6.49E-09	-0.014	0.002	0.696	rs530345654	6	NSF	0	intronic	12.6	6	15	15
rs17692129	17	44793283	C	T	0.340	3.00E-09	-0.014	0.002	0.721	rs530345654	6	NSF	0	intronic	1.4	7	4	5
rs35937770	17	44808360	G	A	0.339	2.50E-09	-0.014	0.002	0.726	rs530345654	6	NSF	0	intronic	6.34	4	4	5
rs530345654	17	44815318	A	ATTG	0.411	8.71E-10	-0.014	0.002	1.000	rs530345654	6	NSF	0	intronic	0.42	NA	4	5
rs17698176	17	44819595	T	G	0.228	6.18E-09	-0.015	0.003	0.863	rs1863115	6	NSF	0	intronic	2.73	5	4	5

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs3809857	17	44848314	G	T	0.331	1.60E-08	-0.013	0.002	0.707	rs530345654	6	WNT3	0	intronic	7.73	4	1	11
rs11697176	20	3831629	C	T	0.106	1.90E-08	-0.021	0.004	1.000	rs11697176	7	MAVS	0	intronic	0.1	6	4	5

Supplementary Table 4. 4: Associations Reported in the GWAS Catalogue[1] for Candidate SNPs in the Discovery GWAS of RTV

[1] www.ebi.ac.uk/gwas/

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
2	rs7684366	4	152737856	rs7684366	2021/06/29	32895543	de la Fuente J	Nat Hum Behav	www.ncbi.nlm.nih.gov/pubmed/32895543	A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data.	Reaction time	
2	rs7684366	4	152749595	rs1385253	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	Reaction time	ENSG00000249184
2	4:152762934_TC_T	4	152768951	rs361212	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	Reaction time	ENSG00000249708
3	rs17167210	7	133054712	rs6950324	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	General cognitive ability	EXOC4
3	rs17167210	7	133055082	rs1149557	2021/01/13	33414549	Demange PA	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/33414549	Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction.	Cognitive aspects of educational attainment	NR
3	rs17167210	7	133055603	rs6973256	2018/02/23	29326435	Hill WD	Mol Psychiatry	www.ncbi.nlm.nih.gov/pubmed/29326435	A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence.	Intelligence (MTAG)	EXOC4
3	rs17167210	7	133055603	rs6973256	2018/09/12	29942086	Savage JE	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/29942086	Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence.	Intelligence	NR

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
3	rs17167210	7	133337635	rs2345941	2020/06/17	32317632	van de Vegte YJ	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/32317632	Genome-wide association studies and Mendelian randomization analyses for leisure sedentary behaviours.	Leisure sedentary behaviour (computer use)	NR
3	rs17167210	7	133339343	rs17167210	2018/02/23	29326435	Hill WD	Mol Psychiatry	www.ncbi.nlm.nih.gov/pubmed/29326435	A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence.	Intelligence (MTAG)	EXOC4
3	rs17167210	7	133341162	rs2483509	2019/08/05	31168069	Ward J	Mol Psychiatry	www.ncbi.nlm.nih.gov/pubmed/31168069	The genomic basis of mood instability: identification of 46 loci in 363,705 UK Biobank participants, genetic correlation with psychiatric disorders, and association with gene expression and function.	Mood instability	EXOC4
3	rs17167210	7	133343353	rs763646	2021/06/29	32895543	de la Fuente J	Nat Hum Behav	www.ncbi.nlm.nih.gov/pubmed/32895543	A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data.	Executive function (trail making test B)	
3	rs17167210	7	133424909	rs12707116	2018/01/12	29186694	Lam M	Cell Rep	www.ncbi.nlm.nih.gov/pubmed/29186694	Large-Scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets.	Cognitive ability	EXOC4
3	rs17167210	7	133424909	rs12707116	2018/01/12	29186694	Lam M	Cell Rep	www.ncbi.nlm.nih.gov/pubmed/29186694	Large-Scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets.	Cognitive ability (MTAG)	EXOC4
3	rs17167210	7	133424909	rs12707116	2018/02/23	29326435	Hill WD	Mol Psychiatry	www.ncbi.nlm.nih.gov/pubmed/29326435	A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence.	Intelligence (MTAG)	EXOC4

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
3	rs17167210	7	133424909	rs12707116	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	General cognitive ability	EXOC4
3	rs17167210	7	133430934	rs1362739	2018/01/12	29186694	Lam M	Cell Rep	www.ncbi.nlm.nih.gov/pubmed/29186694	Large-Scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets.	Cognitive ability	EXOC4
3	rs17167210	7	133430934	rs1362739	2018/09/12	29942086	Savage JE	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/29942086	Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence.	Intelligence	NR
3	rs17167210	7	133430934	rs1362739	2020/01/29	31844048	Hill WD	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/31844048	Genome-wide analysis identifies molecular systems and 149 genetic loci associated with income.	Household income (MTAG)	EXOC4
3	rs17167210	7	133430934	rs1362739	2019/09/04	31374203	Lam M	Am J Hum Genet	www.ncbi.nlm.nih.gov/pubmed/31374203	Pleiotropic Meta-Analysis of Cognition, Education, and Schizophrenia Differentiates Roles of Early Neurodevelopmental and Adult Synaptic Pathways.	Cognitive ability, years of educational attainment or schizophrenia (pleiotropy)	EXOC4
3	rs17167210	7	133535714	rs6972284	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	General cognitive ability	NR
3	rs55812659	7	133582973	rs7793739	2020/01/29	31844048	Hill WD	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/31844048	Genome-wide analysis identifies molecular systems and 149 genetic loci associated with income.	Household income (MTAG)	EXOC4

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
3	rs55812659	7	133606158	rs4422723	2018/02/23	29326435	Hill WD	Mol Psychiatry	www.ncbi.nlm.nih.gov/pubmed/29326435	A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence.	Intelligence (MTAG)	EXOC4
3	rs55812659	7	133611256	rs10263851	2020/10/23	32665545	van der Meer D	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/32665545	Understanding the genetic determinants of the brain with MOSTest.	Brain morphology (MOSTest)	EXOC4
4	rs35859241	15	51741056	rs3751585	2019/02/08	30593698	Hubel C	Am J Med Genet B Neuropsychiatr Genet	www.ncbi.nlm.nih.gov/pubmed/30593698	Genomics of body fat percentage may contribute to sex bias in anorexia nervosa.	Body fat percentage	NR
4	rs35859241	15	51741056	rs3751585	2019/02/08	30593698	Hubel C	Am J Med Genet B Neuropsychiatr Genet	www.ncbi.nlm.nih.gov/pubmed/30593698	Genomics of body fat percentage may contribute to sex bias in anorexia nervosa.	Body fat percentage	NR
4	rs35859241	15	51748146	rs2061425	2018/11/12	30038396	Lee JJ	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30038396	Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals.	Educational attainment (MTAG)	Intergenic
4	rs35859241	15	51934783	rs2252220	2018/11/12	30038396	Lee JJ	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30038396	Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals.	Cognitive performance (MTAG)	Intergenic
4	rs35859241	15	51964210	rs1456297	2018/11/16	30072576	Emilsson V	Science	www.ncbi.nlm.nih.gov/pubmed/30072576	Co-regulatory networks of human serum proteins link genetics to disease.	Blood protein levels	SCG3

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
4	rs35859241	15	51964210	rs1456297	2018/02/23	29326435	Hill WD	Mol Psychiatry	www.ncbi.nlm.nih.gov/pubmed/29326435	A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence.	Intelligence (MTAG)	SCG3
4	rs35859241	15	51964865	rs1378892	2018/07/05	29875488	Sun BB	Nature	www.ncbi.nlm.nih.gov/pubmed/29875488	Genomic atlas of the human plasma proteome.	Blood protein levels	SCG3
4	rs35859241	15	51985564	rs2606146	2018/09/12	29942086	Savage JE	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/29942086	Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence.	Intelligence	NR
5	15:74096786_GA_G	15	74097901	rs16958292	2019/03/18	30643256	Baselmans BML	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30643256	Multivariate genome-wide analyses of the well-being spectrum.	Depressive symptoms	NR
5	15:74096786_GA_G	15	74097901	rs16958292	2019/03/18	30643256	Baselmans BML	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30643256	Multivariate genome-wide analyses of the well-being spectrum.	Well-being spectrum (multivariate analysis)	NR
5	15:74096786_GA_G	15	74097901	rs16958292	2019/03/18	30643256	Baselmans BML	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30643256	Multivariate genome-wide analyses of the well-being spectrum.	Positive affect	NR
5	15:74096786_GA_G	15	74097901	rs16958292	2019/03/18	30643256	Baselmans BML	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30643256	Multivariate genome-wide analyses of the well-being spectrum.	Neuroticism	NR
6	rs1863115	17	44369420	rs7209589	2021/06/29	32895543	de la Fuente J	Nat Hum Behav	www.ncbi.nlm.nih.gov/pubmed/32895543	A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data.	Reaction time	
6	rs1863115	17	44573374	rs2696685	2019/10/16	31562340	Akiyama M	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/31562340	Characterizing rare and low-frequency height-associated variants in the Japanese population.	Height	NSFP1, ARL17A

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
6	rs1863115	17	44623789	rs144216645	2020/09/18	32888494	Vuckovic D	Cell	www.ncbi.nlm.nih.gov/pubmed/32888494	The Polygenic and Monogenic Basis of Blood Traits and Diseases.	Mean corpuscular hemoglobin concentration	ARL17A, LRRC37A2
6	rs1863115	17	44623789	rs144216645	2019/04/17	30980028	de Kovel CGF	Sci Rep	www.ncbi.nlm.nih.gov/pubmed/30980028	The molecular genetics of hand preference revisited.	Handedness (Left-handed vs. non-left-handed)	STH, KANSL1, ARL17B, ARL17A, LRRC37A, LRRC37A2, NSF
6	rs1863115	17	44623789	rs144216645	2019/04/17	30980028	de Kovel CGF	Sci Rep	www.ncbi.nlm.nih.gov/pubmed/30980028	The molecular genetics of hand preference revisited.	Handedness (Right-handed vs. non-right-handed)	STH, KANSL1, ARL17B, ARL17A, LRRC37A, LRRC37A2, NSF
6	rs1863115	17	44625928	rs1863115	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	General cognitive ability	NR
6	rs1863115	17	44625928	rs1863115	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	Reaction time	LRRC37A2
6	rs1863115	17	44652348	rs558710130	2020/09/21	32888493	Chen MH	Cell	www.ncbi.nlm.nih.gov/pubmed/32888493	Trans-ethnic and Ancestry-Specific Blood-Cell Genetics in 746,667	Mean corpuscular hemoglobin	NR

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
										Individuals from 5 Global Populations.	concentration	
6	rs1863115	17	44652651	rs112458826	2020/09/21	32888493	Chen MH	Cell	www.ncbi.nlm.nih.gov/pubmed/32888493	Trans-ethnic and Ancestry-Specific Blood-Cell Genetics in 746,667 Individuals from 5 Global Populations.	Monocyte count	NR
6	rs530345654	17	44793283	rs17692129	2020/07/20	32198502	Shin J	Cereb Cortex	www.ncbi.nlm.nih.gov/pubmed/32198502	Global and Regional Development of the Human Cerebral Cortex: Molecular Architecture and Occupational Aptitudes.	Cortical surface area (global PC1)	NSF
6	rs530345654	17	44793283	rs17692129	2018/10/31	29942085	Nagel M	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/29942085	Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways.	Neuroticism	NR
6	rs530345654	17	44793283	rs17692129	2019/03/28	30643251	Liu M	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30643251	Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use.	Smoking initiation (ever regular vs never regular)	NR
6	rs530345654	17	44808360	rs35937770	2020/07/21	32193296	Grasby KL	Science	www.ncbi.nlm.nih.gov/pubmed/32193296	The genetic architecture of the human cerebral cortex.	Cortical surface area	NR
6	rs530345654	17	44808360	rs35937770	2018/09/17	29844566	Davies G	Nat Commun	www.ncbi.nlm.nih.gov/pubmed/29844566	Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function.	Reaction time	NSF
6	rs1863115	17	44819595	rs17698176	2020/01/28	31676860	Zhao B	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/31676860	Genome-wide association analysis of 19,629 individuals identifies variants influencing regional brain volumes and refines their genetic	Brain region volumes	NR

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
										co-architecture with cognitive and mental health traits.		
6	rs1863115	17	44819595	rs17698176	2018/09/12	29942086	Savage JE	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/29942086	Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence.	Intelligence	NR
6	rs1863115	17	44819595	rs17698176	2018/10/31	29942085	Nagel M	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/29942085	Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways.	Neuroticism	NR
6	rs1863115	17	44819595	rs17698176	2021/06/29	32895543	de la Fuente J	Nat Hum Behav	www.ncbi.nlm.nih.gov/pubmed/32895543	A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data.	Cognitive traits (MTAG)	
6	rs1863115	17	44833217	rs35732828	2021/06/29	33462484	Sinnott-Armstrong N	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/33462484	Genetics of 35 blood and urine biomarkers in the UK Biobank.	Glycated hemoglobin levels	NR
6	rs530345654	17	44848314	rs3809857	2017/10/09	28199695	Jones AV	Hum Mol Genet	www.ncbi.nlm.nih.gov/pubmed/28199695	GWAS of self-reported mosquito bite size, itch intensity and attractiveness to mosquitoes implicates immune-related predisposition loci.	Itch intensity from mosquito bite adjusted by bite size	WNT3
6	rs530345654	17	44848314	rs3809857	2019/03/28	30643251	Liu M	Nat Genet	www.ncbi.nlm.nih.gov/pubmed/30643251	Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use.	Smoking initiation (ever regular vs never regular) (MTAG)	NR

Genomic Locus	Independent Significant SNP	CHR	BP	SNP	Date Added To Catalogue	PMID	First Author	Journal	Link	Study	Trait	Reported Gene
6	rs530345654	17	44848314	rs3809857	2021/08/24	34021172	Christakoudi S	Sci Rep	www.ncbi.nlm.nih.gov/pubmed/34021172	GWAS of allometric body-shape indices in UK Biobank identifies loci suggesting associations with morphogenesis, organogenesis, adrenal cell renewal and cancer.	Hip circumference adjusted for BMI	WNT3

Note. *CHR* chromosome, *BP* base pair, *PMID* Pubmed identity

Supplementary Table 4. 5: Summary Statistics and Functional Annotation for Reaching Genome-wide Significance in the Meta-analysis of the Discovery and Replication GWAS

Note: The effect size (BETA) and standard error (SE) are given for the effect allele (A1) in the meta-analysis of the discovery and replication GWAS using METAL. Independent (r2 < .1) lead snps in a region are in red. MAF = minor allele frequency based on the 1000 Genomes Project Phase 3 release all populations reference panel. ANNOVAR = functional variant classification based on position in or outside of a gene; CADD = Combined Annotation-Dependent depletion score, ; RDB = RegulomeDB scores; minChrState = minimum chromatin state across 127 tissue types ; commonChrState = most common chromatin state in 127 tissue types.

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs183204237	2	162188514	G	C	0.001	2.95 E-08	-0.199	0.036	1.000	rs183204237	1	PSMD14	0	intronic	3.465	5	4	5
rs7684366	4	152737856	C	T	0.296	1.90 E-09	0.015	0.003	1.000	rs7684366	2	RP11-424M21.1	15355	intergenic	1.473	6	5	15
rs2136959	4	152740233	G	A	0.298	6.94 E-09	0.014	0.003	0.976	rs7684366	2	RP11-424M21.1	17732	intergenic	0.511	7	9	15
rs1385253	4	152749595	C	T	0.296	4.26 E-09	0.015	0.003	0.969	rs7684366	2	RP11-424M21.1	27094	intergenic	0.714	7	14	15
rs361199	4	152757511	T	A	0.473	2.46 E-08	0.013	0.002	0.613	4:152757519_GTT_G	2	RP11-424M21.1	35010	intergenic	0.568	6	5	15
4:152757519_GTT_G	4	152757519	GTT	G	0.350	1.31 E-08	-0.012	0.002	1.000	4:152757519_GTT_G	2	RP11-424M21.1	35018	intergenic	0.766	NA	5	15
rs361200	4	152758061	T	A	0.412	3.60 E-08	0.012	0.002	0.742	4:152757519_GTT_G	2	RP11-424M21.1	35560	intergenic	2.056	7	5	15
rs181731	4	152759119	C	T	0.413	3.55 E-08	0.012	0.002	0.740	4:152757519_GTT_G	2	RP11-424M21.1	36618	intergenic	0.207	7	5	15
rs361205	4	152759751	C	T	0.412	2.00 E-08	-0.012	0.002	0.742	4:152757519_GTT_G	2	RP11-424M21.1	37250	intergenic	0.503	6	5	15
rs361206	4	152759925	C	A	0.412	1.93 E-08	-0.012	0.002	0.743	4:152757519_GTT_G	2	RP11-424M21.1	37424	intergenic	0.143	6	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs361207	4	152760129	G	A	0.413	2.86 E-08	0.012	0.002	0.745	4:152757519_ GTT_G	2	RP11-424M21.1	37628	intergenic	0.932	7	5	15
rs10000280	4	152760983	G	C	0.413	2.64 E-08	-0.012	0.002	0.742	4:152757519_ GTT_G	2	RP11-424M21.1	38482	intergenic	0.262	7	5	15
rs191716	4	152761365	C	T	0.412	2.96 E-08	-0.012	0.002	0.743	4:152757519_ GTT_G	2	RP11-424M21.1	38864	intergenic	2.879	6	5	15
rs361191	4	152761633	G	T	0.413	3.03 E-08	0.012	0.002	0.744	4:152757519_ GTT_G	2	RP11-424M21.1	39132	intergenic	4.542	6	5	15
rs361194	4	152762925	G	T	0.462	1.75 E-08	-0.013	0.002	0.639	4:152757519_ GTT_G	2	RP11-424M21.1	40424	intergenic	1.096	NA	5	15
rs35206686	4	152762934	TC	T	0.456	1.55 E-08	-0.013	0.002	0.629	4:152757519_ GTT_G	2	RP11-424M21.1	40433	intergenic	1.721	NA	5	15
rs361197	4	152763556	G	A	0.464	4.99 E-08	0.013	0.002	0.636	4:152757519_ GTT_G	2	RP11-424M21.1	41055	intergenic	3.91	5	5	15
rs361212	4	152768951	C	T	0.417	7.57 E-09	0.014	0.002	0.644	rs361209	2	RP11-503L23.1	39743	intergenic	1.885	7	5	15
rs189679	4	152775454	G	C	0.252	2.47 E-08	0.014	0.003	1.000	rs189679	2	RP11-503L23.1	33240	intergenic	0.592	7	5	15
rs361209	4	152776538	G	A	0.386	6.86 E-09	-0.014	0.002	1.000	rs361209	2	RP11-503L23.1	32156	intergenic	2.283	6	5	15
rs244404	4	152778727	C	A	0.401	1.21 E-08	-0.013	0.002	0.946	rs361209	2	RP11-503L23.1	29967	intergenic	0.766	5	1	15
rs536439	4	152780684	T	A	0.386	1.33 E-08	0.013	0.002	0.992	rs361209	2	RP11-503L23.1	28010	intergenic	3.139	5	5	15
rs528612	4	152781361	C	T	0.376	1.11 E-08	0.014	0.002	0.953	rs361209	2	RP11-503L23.1	27333	intergenic	0.891	6	5	15
7:133532290_ ATT_A	7	133532290	ATT	A	0.433	3.45 E-08	-0.012	0.002	1.000	7:133532290_ ATT_A	3	EXOC4	0	intronic	0.115	NA	5	15
rs55812659	7	133608748	GT	G	0.472	4.67 E-08	0.012	0.002	1.000	rs55812659	3	EXOC4	0	intronic	0.398	NA	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs912243472	15	74096786	GA	G	0.248	4.82E-08	0.017	0.003	0.972	rs9920550	4	RP11-8P11.3	34807	intergenic	2.114	NA	5	15
rs12442263	15	74099391	G	T	0.245	4.98E-08	0.017	0.003	0.997	rs9920550	4	RP11-8P11.3	37412	intergenic	4.282	4	2	15
rs9920550	15	74100696	C	A	0.245	4.67E-08	-0.017	0.003	1.000	rs9920550	4	RP11-8P11.3	38717	intergenic	4.079	7	5	15
rs7209589	17	44369420	G	A	0.360	1.93E-09	-0.016	0.003	1.000	rs7209589	5	ARL17B	0	intronic	0.796	7	5	15
rs536912361	17	44382820	G	A	0.099	1.75E-08	0.016	0.003	1.000	rs536912361	5	ARL17B:LRRC37A	00:00	intronic	0.802	NA	15	15
rs273534	17	44410179	C	T	0.383	3.58E-09	-0.016	0.003	0.744	rs1863115	5	ARL17B:LRRC37A	00:00	intronic	1.774	6	5	15
rs2137113	17	44410368	G	T	0.410	5.31E-09	-0.015	0.003	0.723	rs1863115	5	ARL17B:LRRC37A	00:00	intronic	13.19	6	5	15
rs144216645	17	44623789	C	T	0.437	1.18E-08	-0.014	0.003	0.673	rs1863115	5	LRRC37A2:ARL17A	00:00	intronic	9.897	6	5	15
rs1863115	17	44625928	C	A	0.365	5.63E-10	0.016	0.003	1.000	rs1863115	5	LRRC37A2:ARL17A	00:00	exonic	18.32	6	5	15
rs147382204	17	44768597	G	T	0.200	8.22E-09	0.013	0.002	0.946	rs17692129	5	NSF	0	intronic	12.64	6	15	15
rs17692129	17	44793283	C	T	0.200	4.29E-09	-0.013	0.002	1.000	rs17692129	5	NSF	0	intronic	1.397	7	4	5
rs35937770	17	44808360	G	A	0.200	4.54E-09	-0.013	0.002	0.981	rs17692129	5	NSF	0	intronic	6.343	4	4	5
rs530345654	17	44815318	ATTG	A	0.425	3.82E-10	0.014	0.002	1.000	rs530345654	5	NSF	0	intronic	0.419	NA	4	5
rs17698176	17	44819595	G	T	0.082	2.26E-08	0.014	0.003	0.601	rs536912361	5	NSF	0	intronic	2.727	5	4	5
rs3809857	17	44848314	G	T	0.200	3.83E-08	-0.012	0.002	0.918	rs17692129	5	WNT3	0	intronic	7.728	4	1	11

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs149388786	19	37063610	TT TA TC TA TC	T	0.079	2.90 E-08	-0.015	0.003	1.000	rs149388786	6	ZNF529	0	intronic	1.669	NA	1	1

Supplementary Table 4. 6: Genome-wide Significant ($p < 2.61 \times 10^{-6}$) Genes Identified in MAGMA Analysis of the Discovery RTV GWAS

Gene	Chromosome	Start	Stop	Number of SNPs	*P*
EXOC4	7	132937829	133751342	3536	6.30×10^{-07}
TBC1D21	15	74165949	74181555	79	2.57×10^{-06}
CNTNAP4	16	76311176	76593135	1966	2.59×10^{-07}
LRRC37A	17	44370099	44415160	13	9.81×10^{-10}
NSF	17	44668035	44834830	168	4.97×10^{-07}

Supplementary Table 4. 7: Identified Genes from the Discovery RTV GWAS Used as Input for Gene-set Enrichment Analysis

Ensembl ID	Gene Symbol
ENSG00000186417	*GLDN*
ENSG00000104093	*DMXL2*
ENSG00000104112	*SCG3*
ENSG00000140280	*LYSMD2*
ENSG00000205363	*C15orf59*
ENSG00000167139	*TBC1D21*
ENSG00000152910	*CNTNAP4*
ENSG00000120088	*CRHR1*
ENSG00000228696	*ARL17B*
ENSG00000176681	*LRRC37A*
ENSG00000238083	*LRRC37A2*
ENSG00000185829	*ARL17A*
ENSG00000073969	*NSF*
ENSG00000108379	*WNT3*
ENSG00000158955	*WNT9B*
ENSG00000004897	*CDC27*
ENSG00000259207	*ITGB3*
ENSG00000259753	*ITGB3*
ENSG00000178852	*EFCAB13*
ENSG00000141279	*NPEPPS*
ENSG00000115233	*PSMD14*
ENSG00000136535	*TBR1*
ENSG00000144290	*SLC4A10*
ENSG00000088888	*MAVS*
ENSG00000125779	*PANK2*

Ensembl ID	Gene Symbol
ENSG00000164142	*FAM160A1*
ENSG00000131558	*EXOC4*

Supplementary Table 4. 8: Results Showing the Genetic Correlations Between RTV, Mean RT, and Selected Traits

	Estimates for RTV				*Estimates for Mean RT*				*Difference Between rg_{RTV} vs $rg_{Mean\ RT}$*	
Trait	**rg**	**SE**	***P***		**rg**	**SE**	***P***		***z* Score**	***P***
Educational attainment	-0.232	0.026	<2.2E-16		-0.073	0.018	7.71E-05		-5.028	4.96E-07
General cognitive ability	-0.436	0.028	<2.2E-16		-0.179	0.022	6.44E-16		-7.212	5.30E-13
Mean reaction time	0.687	0.022	<2.2E-16		NA	NA	NA		NA	NA
RTV	NA	NA	NA		0.687	0.022	<2.2E-16		NA	NA
Intraindividual coefficient of variation	0.889	0.009	<2.2E-16		NA	NA	NA		NA	NA
Neuroticism	0.134	0.028	2.27E-06		0.067	0.024	5.30E-03		1.817	6.92E-02
Alzheimer's Disease	0.030	0.062	6.28E-01		0.080	0.050	1.13E-01		-0.628	5.30E-01
ADHD	0.104	0.022	5.10E-03		-0.064	0.029	2.47E-02		4.615	3.92E-06
PTSD	0.150	0.073	3.99E-02		0.011	0.053	8.34E-01		1.538	1.24E-01
Schizophrenia	0.265	0.027	<2.2E-16		0.237	0.022	<2.2E-16		0.804	4.21E-01
Intracranial volume	-0.076	0.100	4.49E-01		-0.023	0.070	7.46E-01		-0.434	6.64E-01
Cortical surface area	-0.089	0.040	2.66E-02		-0.041	0.034	2.30E-01		-0.914	3.61E-01
Cortical thickness	-0.079	0.049	1.09E-01		-0.018	0.034	5.88E-01		-1.023	3.06E-01
Nucleus accumbens	-0.120	0.054	2.68E-02		-0.077	0.041	6.37E-02		-0.634	5.26E-01
Amygdala	-0.157	0.071	2.78E-02		-0.048	0.056	3.92E-01		1.205	2.28E-01
Brainstem	-0.146	0.054	7.10E-03		-0.150	0.043	4.00E-04		0.058	9.54E-01
Caudate Nucleus	-0.102	0.044	1.91E-02		-0.032	0.037	3.79E-01		-1.222	2.22E-01
Pallidum	-0.111	0.062	7.25E-02		-0.191	0.047	4.90E-05		1.028	3.04E-01
Putamen	-0.100	0.048	3.56E-02		-0.048	0.039	2.17E-01		-0.841	4.00E-01
Thalamus	-0.094	0.053	7.83E-02		-0.169	0.046	3.00E-03		1.069	2.85E-01

Note. rg genetic correlation, *SE* standard error

Supplementary Table 4. 9: Results from Linear Regression Analyses to Assess the Relationship Between RTV and Selected Phenotypes in the UK Biobank

Trait	Standardized Beta	SE	*P*
Educational attainment	-0.047	0.002	<2.2E-16
General cognitive ability	-0.136	0.002	<2.2E-16
Mean reaction time	0.440	0.001	<2.2E-16
Intraindividual coefficient of variation	0.877	0.001	<2.2E-16
Neuroticism	0.034	0.002	<2.2E-16
Alzheimer's Disease	0.175	0.021	<2.2E-16
ADHD	0.023	0.086	7.90E-01
PTSD	0.210	0.044	1.76E-06
Schizophrenia	0.345	0.030	<2.2E-16
Intracranial volume	-0.029	0.006	3.97E-07
Cortical surface area	-0.023	0.006	5.38E-05
Cortical thickness	-0.116	0.005	3.17E-02
Nucleus accumbens	0.000	0.005	9.46E-01
Amygdala	0.000	0.006	9.69E-01
Brainstem	-0.009	0.006	1.60E-01
Caudate Nucleus	-0.010	0.006	7.75E-02
Pallidum	-0.010	0.006	6.42E-02
Putamen	0.000	0.005	9.80E-01
Thalamus	-0.009	0.007	1.63E-01

Note. SE standard error

Supplementary Table 4. 10: Summary Statistics and Functional Annotation for SNPs Reaching Genome-wide Significance in ICV-GWAS

Note: The effect size (BETA) and standard error (SE) are given for the effect allele (A1) in the ICV-GWAS in 405,302 inidividuals. MAF = minor allele frequency based on the 1000 Genomes Project Phase 3 release European reference panel. ANNOVAR = functional variant classification based on position in or outside of a gene; CADD = Combined Annotation-Dependent depletion score, ; RDB = RegulomeDB scores; minChrState = minimum chromatin state across 127 tissue types ; commonChrState = most common chromatin state in 127 tissue types.

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs183204237	2	162188514	G	C	0.003	3.10 E-08	-0.211	0.038	1.000	rs183204237	1	PSMD14	0	intronic	3.465	5	4	5
rs2345941	7	133337635	A	G	0.452	1.20 E-08	0.013	0.002	0.905	rs17167210	2	EXOC4	0	intronic	2.072	5	5	15
rs2066924	7	133338462	C	A	0.448	1.07 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	2.664	NA	5	15
rs17167210	7	133339343	G	A	0.431	1.02 E-09	0.014	0.002	1.000	rs17167210	2	EXOC4	0	intronic	1.221	5	5	15
rs2483507	7	133339546	C	T	0.448	1.19 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	2.778	5	5	15
rs2483509	7	133341162	G	A	0.451	7.92 E-09	0.013	0.002	0.924	rs17167210	2	EXOC4	0	intronic	0.9	6	5	15
rs12530581	7	133342955	A	T	0.448	1.25 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.309	7	5	15
rs763643	7	133343243	T	A	0.448	1.19 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	6.268	5	5	15
rs763644	7	133343349	G	C	0.448	1.16 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.836	5	5	15
rs763646	7	133343353	C	T	0.448	1.63 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	3.231	5	5	15
rs763645	7	133343428	C	T	0.448	1.24 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.671	7	5	15
rs6970448	7	133343642	G	A	0.448	1.21 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.8	6	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs4731974	7	133344010	C	T	0.448	1.20 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	2.686	6	5	15
rs4728296	7	133344566	C	T	0.448	1.53 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.203	7	5	15
rs7776986	7	133345635	C	T	0.449	1.24 E-08	-0.013	0.002	0.931	rs17167210	2	EXOC4	0	intronic	9.946	5	5	15
rs10236819	7	133345983	A	T	0.448	1.38 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.863	7	5	15
rs10266435	7	133346081	C	T	0.448	1.62 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	0.453	7	5	15
rs1133540	7	133346380	C	T	0.448	1.39 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	1.319	7	5	15
rs17601462	7	133347066	A	G	0.448	1.61 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	7.755	7	5	15
rs10231828	7	133348337	T	G	0.450	1.23 E-08	0.013	0.002	0.927	rs17167210	2	EXOC4	0	intronic	2.588	6	4	15
rs10231829	7	133348338	T	A	0.450	1.23 E-08	0.013	0.002	0.927	rs17167210	2	EXOC4	0	intronic	1.264	6	4	15
rs2430769	7	133349149	G	A	0.449	9.62 E-09	0.013	0.002	0.931	rs17167210	2	EXOC4	0	intronic	4.689	5	5	15
rs1014442	7	133349281	A	T	0.448	1.22 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	1.185	5	5	15
rs10808271	7	133352318	T	C	0.448	1.52 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	4.045	5	5	15
rs1041621	7	133353965	G	A	0.448	1.44 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	2.093	NA	5	15
rs17659708	7	133355098	A	G	0.448	1.44 E-08	0.013	0.002	0.934	rs17167210	2	EXOC4	0	intronic	1.091	4	5	15
rs62471409	7	133371246	C	T	0.430	1.03 E-08	0.013	0.002	0.848	rs17167210	2	EXOC4	0	intronic	0.27	7	5	15
rs1833334	7	133371836	C	T	0.430	1.13 E-08	0.013	0.002	0.848	rs17167210	2	EXOC4	0	intronic	0.375	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs2041996	7	133390510	G	A	0.429	2.04 E-08	0.012	0.002	0.844	rs17167210	2	EXOC4	0	intronic	2.732	4	2	15
rs2016876	7	133395492	T	G	0.429	1.74 E-08	0.013	0.002	0.844	rs17167210	2	EXOC4	0	intronic	5.809	5	5	15
rs12707117	7	133429058	G	A	0.432	1.50 E-08	-0.013	0.002	0.841	rs17167210	2	EXOC4	0	intronic	0.002	7	5	15
rs11768260	7	133430482	T	C	0.424	2.86 E-08	0.012	0.002	0.820	rs17167210	2	EXOC4	0	intronic	0.901	6	5	15
rs10954431	7	133430901	G	T	0.429	1.14 E-08	0.013	0.002	0.844	rs17167210	2	EXOC4	0	intronic	1.495	7	5	15
rs10247014	7	133431038	G	T	0.430	1.28 E-08	0.013	0.002	0.848	rs17167210	2	EXOC4	0	intronic	2.202	6	5	15
rs9649046	7	133433402	G	A	0.429	1.24 E-08	0.013	0.002	0.844	rs17167210	2	EXOC4	0	intronic	2.046	4	5	15
rs2551023	7	133472662	A	C	0.456	1.10 E-08	0.013	0.002	0.757	rs17167210	2	EXOC4	0	intronic	2.815	NA	5	15
rs2113336	7	133478107	C	A	0.453	9.63 E-09	0.013	0.002	0.760	rs17167210	2	EXOC4	0	intronic	0.86	NA	5	15
rs2542274	7	133491069	C	T	0.453	1.48 E-08	0.013	0.002	0.760	rs17167210	2	EXOC4	0	intronic	2.207	7	5	15
rs2550986	7	133501113	G	A	0.454	9.49 E-09	0.013	0.002	0.759	rs55812659	2	EXOC4	0	intronic	2.416	NA	5	15
rs34678688	7	133504607	A	AC	0.454	1.03 E-08	-0.013	0.002	0.759	rs55812659	2	EXOC4	0	intronic	3.23	NA	4	5
rs7786100	7	133505716	G	T	0.457	1.82 E-08	-0.013	0.002	0.753	rs17167210	2	EXOC4	0	intronic	1.594	5	4	5
rs6944452	7	133522387	A	G	0.454	8.72 E-09	-0.013	0.002	0.750	rs17167210	2	EXOC4	0	intronic	1.949	3a	5	15
rs7802352	7	133523259	T	C	0.451	1.15 E-08	-0.013	0.002	0.753	rs17167210	2	EXOC4	0	intronic	1.496	7	5	15
7:133532290_ ATT_A	7	133532290	AT T	A	0.497	6.79 E-09	-0.013	0.002	0.649	rs17167210	2	EXOC4	0	intronic	0.115	NA	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs6972284	7	133535714	T	C	0.453	2.47 E-08	-0.012	0.002	0.760	rs17167210	2	EXOC4	0	intronic	8.664	5	5	15
rs6954207	7	133560955	C	T	0.459	1.42 E-08	-0.013	0.002	0.756	rs55812659	2	EXOC4	0	intronic	6.543	5	5	15
rs6954859	7	133561464	A	G	0.454	1.43 E-08	-0.013	0.002	0.761	rs55812659	2	EXOC4	0	intronic	1.808	5	5	15
rs12707124	7	133566423	T	C	0.455	1.01 E-08	-0.013	0.002	0.763	rs55812659	2	EXOC4	0	intronic	4.504	5	5	15
rs10156038	7	133570725	T	A	0.458	7.83 E-09	-0.013	0.002	0.754	rs55812659	2	EXOC4	0	intronic	1.357	5	5	15
rs12707125	7	133570858	A	G	0.457	8.96 E-09	-0.013	0.002	0.760	rs55812659	2	EXOC4	0	intronic	3.175	5	5	15
rs6967343	7	133571797	A	G	0.454	6.69 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	7.408	5	5	15
rs6467506	7	133572410	A	G	0.454	8.03 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	8.534	4	5	15
rs56255935	7	133572945	T	TC CC	0.457	1.30 E-08	-0.013	0.002	0.760	rs55812659	2	EXOC4	0	intronic	2.134	NA	5	15
rs10246164	7	133573039	T	C	0.457	8.33 E-09	-0.013	0.002	0.760	rs55812659	2	EXOC4	0	intronic	14.29	5	5	15
rs10246406	7	133573222	T	A	0.457	8.38 E-09	-0.013	0.002	0.760	rs55812659	2	EXOC4	0	intronic	9.745	4	5	15
rs10231158	7	133573540	C	G	0.457	9.67 E-09	-0.013	0.002	0.760	rs55812659	2	EXOC4	0	intronic	5.309	5	5	15
rs6978533	7	133574051	A	C	0.454	7.68 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.663	7	5	15
rs201882079	7	133577600	T	A	0.458	1.31 E-08	-0.013	0.002	0.753	rs55812659	2	EXOC4	0	intronic	3.623	7	5	15
rs199741058	7	133578800	G	A	0.451	1.85 E-08	-0.013	0.002	0.756	rs55812659	2	EXOC4	0	intronic	2.562	7	5	15
rs201376358	7	133579006	T	C	0.460	2.04 E-08	-0.012	0.002	0.750	rs55812659	2	EXOC4	0	intronic	4.065	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs7788061	7	133579844	T	C	0.458	1.08 E-08	-0.013	0.002	0.763	rs55812659	2	EXOC4	0	intronic	3.61	7	5	5
rs7805268	7	133579980	G	A	0.455	1.18 E-08	-0.013	0.002	0.765	rs55812659	2	EXOC4	0	intronic	3.268	6	5	5
rs2042454	7	133580710	A	G	0.454	9.49 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	5.207	NA	4	5
rs2042452	7	133581093	A	G	0.454	1.04 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	11.01	NA	4	5
rs2288067	7	133581102	A	G	0.454	9.65 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	13.75	NA	4	5
7:133581274_ AG_A	7	133581274	A G	A	0.455	1.10 E-08	-0.013	0.002	0.771	rs55812659	2	EXOC4	0	intronic	0.312	NA	4	5
rs6467507	7	133581480	A	G	0.455	6.07 E-09	-0.013	0.002	0.765	rs55812659	2	EXOC4	0	intronic	0.443	7	4	5
rs7794229	7	133581563	T	C	0.454	1.22 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	0.469	6	4	5
rs13309851	7	133582364	C	A	0.457	7.52 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	0.448	5	4	5
rs777716181	7	133582502	CT	C	0.457	7.01 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	0.667	NA	5	5
rs7793582	7	133582851	G	A	0.457	7.14 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	2.858	6	5	5
rs7793732	7	133582953	G	T	0.457	7.19 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	0.746	7	5	5
rs7793739	7	133582973	G	T	0.457	7.06 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	2.484	7	5	5
rs7776858	7	133583144	T	C	0.457	7.19 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	2.56	6	5	5
rs7793959	7	133583280	C	T	0.457	8.77 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	3.609	6	5	5
rs112523920	7	133583296	A	A G	0.455	7.46 E-09	-0.013	0.002	0.771	rs55812659	2	EXOC4	0	intronic	0.876	NA	5	5

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
				AC CA TC CT G														
rs13312097	7	133583603	T	C	0.457	7.37 E-09	-0.013	0.002	0.757	rs55812659	2	EXOC4	0	intronic	0.114	7	5	15
rs7798192	7	133583841	A	T	0.454	8.64 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	0.973	5	5	15
rs7798355	7	133583899	A	G	0.454	8.64 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	5.72	5	5	15
rs7798673	7	133584077	C	T	0.454	8.58 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.124	4	5	15
rs12707126	7	133584271	A	G	0.454	1.38 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.421	5	5	15
rs6971638	7	133585386	A	G	0.454	8.60 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	7.845	7	5	15
rs6971840	7	133585570	A	G	0.454	8.45 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	7.282	6	5	15
rs6954537	7	133585612	T	C	0.454	8.08 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	5.957	6	5	15
rs6972423	7	133585678	G	A	0.454	8.47 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.773	7	5	15
rs6976416	7	133585752	G	A	0.454	8.21 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.146	7	5	15
rs6976885	7	133585989	G	A	0.453	8.56 E-09	-0.013	0.002	0.766	rs55812659	2	EXOC4	0	intronic	13.89	7	5	15
rs12707127	7	133586089	A	G	0.454	8.45 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	3.869	7	5	15
rs7782545	7	133587689	C	T	0.454	9.04 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.658	7	5	15

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs7783179	7	133588117	C	G	0.454	9.13 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.031	7	5	15
rs10241782	7	133588380	A	G	0.455	8.80 E-09	-0.013	0.002	0.765	rs55812659	2	EXOC4	0	intronic	4.043	5	5	15
rs10271671	7	133588413	G	A	0.455	8.84 E-09	-0.013	0.002	0.765	rs55812659	2	EXOC4	0	intronic	6.544	5	5	15
rs6950081	7	133588565	A	G	0.454	8.48 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	0.369	7	5	15
rs6974386	7	133588738	T	C	0.454	8.48 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	6.4	6	4	15
rs6954999	7	133588927	G	A	0.454	8.22 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	3.507	7	4	15
rs6955061	7	133589145	C	T	0.454	8.56 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	4.219	7	4	15
rs6975860	7	133589584	T	G	0.454	8.36 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	15.46	5	4	15
rs6956135	7	133589608	G	T	0.454	8.50 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	13.92	5	4	15
rs1862873	7	133590287	T	A	0.455	1.02 E-08	-0.013	0.002	0.765	rs55812659	2	EXOC4	0	intronic	0.766	7	4	15
rs2113339	7	133591473	A	G	0.454	1.39 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	3.472	NA	4	15
rs2113338	7	133591539	T	C	0.454	1.09 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.987	NA	4	15
rs2042451	7	133593030	A	G	0.454	1.03 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.653	6	5	15
rs1593171	7	133597442	G	C	0.454	1.10 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	3.779	7	1	15
rs5887650	7	133602902	A	AT	0.454	1.02 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.529	NA	4	5
rs1862872	7	133602934	A	C	0.454	9.69 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.518	NA	4	5

SNP	CHR	BP	A2	A1	MAF	P	BETA	SE	r^2	IndSigSNP	Locus	Nearest Gene	Gene Distance	ANNOVAR Category	CADD	RDB	minChrState	commonChrState
rs751967768	7	133603493	TA	T	0.454	9.68 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	2.137	NA	4	5
rs4422723	7	133606158	A	T	0.454	1.34 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	5.568	7	4	8
rs4517044	7	133607014	T	A	0.454	1.23 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.316	5	5	15
rs1963841	7	133607535	A	G	0.454	1.35 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	1.983	NA	5	15
7:133607740_GT_G	7	133607740	GT	G	0.455	8.20 E-09	-0.013	0.002	0.763	rs55812659	2	EXOC4	0	intronic	0.509	NA	5	15
rs55812659	7	133608748	G	GT	0.479	5.04 E-09	-0.013	0.002	1.000	rs55812659	2	EXOC4	0	intronic	0.398	NA	5	15
rs10263851	7	133611256	C	T	0.454	1.38 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	0.628	6	5	15
7:133614230_GA_G	7	133614230	GA	G	0.452	1.06 E-08	-0.013	0.002	0.752	rs55812659	2	EXOC4	0	intronic	1.897	NA	5	15
rs6970436	7	133614710	A	G	0.454	1.16 E-08	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	0.975	7	5	15
rs1025074	7	133615559	G	A	0.453	9.43 E-09	-0.013	0.002	0.765	rs55812659	2	EXOC4	0	intronic	0.855	NA	5	15
7:133617799_AT_A	7	133617799	AT	A	0.442	8.04 E-09	-0.013	0.002	0.704	rs55812659	2	EXOC4	0	intronic	0.581	NA	4	15
rs6954610	7	133618986	A	G	0.454	9.70 E-09	-0.013	0.002	0.769	rs55812659	2	EXOC4	0	intronic	12.57	7	5	15
rs2470166	15	51708602	A	C	0.212	3.27 E-08	-0.014	0.003	0.939	rs35859241	3	RP11-707P17.1	0	ncRNA_intronic	6.661	NA	5	15
rs8026587	15	51736411	C	T	0.220	4.15 E-09	-0.015	0.003	0.983	rs35859241	3	RP11-707P17.1	0	ncRNA_intronic	11.36	4	5	15
rs35859241	15	51736660	A	G	0.221	1.85 E-09	-0.015	0.003	1.000	rs35859241	3	RP11-707P17.1	0	ncRNA_intronic	0.517	7	5	15
rs149388786	19	37063610	T	TTTA	0.183	2.59 E-08	0.016	0.003	1.000	rs149388786	4	ZNF529	0	intronic	1.669	NA	1	1

commonChrState	
minChrState	
RDB	
CADD	
ANNOVAR Category	
Gene Distance	
Nearest Gene	
Locus	
IndSigSNP	
r^2	
SE	
BETA	
P	
MAF	
A1	TC TA TC
A2	
BP	
CHR	
SNP	

Supplementary Table 4. 11: Polygenic Scores Derived from Discovery GWAS Predicting RTV in Five Independent Samples of Diverse ancestry

Target cohort: UKB EUR			*Target cohort: UKB SAS*			*Target cohort: UKB AFR*			*Target cohort: TOP EUR*			*Target cohort: SAX AFR*		
N=26,692			*N = 7,974*			*N = 6,535*			*N = 182*			*N = 563*		
PRSice Scores														
Threshold	***P***	**R^2**	**Threshold**	***P***	**R^2**	**Threshold**	***P***	**R^2**	**Threshold**	***P***	**R^2**	**Threshold**	***P***	**R^2**
5,00E-08	0,32	0,000	5,00E-08	0,32	0,000	5,00E-08	0,24	0,000	5,00E-08	0,69	0,001	5,00E-08	0,61	0,000
1,00E-07	0,25	0,000	1,00E-07	0,36	0,000	1,00E-07	0,20	0,000	1,00E-07	0,64	0,001	1,00E-07	0,82	0,000
1,00E-06	0,10	0,000	1,00E-06	0,89	0,000	1,00E-06	0,02	0,001	1,00E-06	0,28	0,007	1,00E-06	0,96	0,000
1,00E-05	4,60E-04	0,000	1,00E-05	0,88	0,000	1,00E-05	0,34	0,000	1,00E-05	0,61	0,001	1,00E-05	0,90	0,000
1,00E-04	5,77E-04	0,000	1,00E-04	0,52	0,000	1,00E-04	0,72	0,000	1,00E-04	0,99	0,000	1,00E-04	0,26	0,002
1,00E-03	1,00E-06	0,001	1,00E-03	0,97	0,000	1,00E-03	0,89	0,000	1,00E-03	0,93	0,000	1,00E-03	0,28	0,002
0,01	4,19E-13	0,002	0,01	0,05	0,000	0,01	0,30	0,000	0,01	0,23	0,008	0,01	0,91	0,000
0,05	3,91E-17	0,003	0,05	0,04	0,001	0,05	0,08	0,000	0,05	0,62	0,001	0,05	0,44	0,001
0,1	3,80E-17	0,003	0,1	0,08	0,000	0,1	0,12	0,000	0,1	0,77	0,000	0,1	0,49	0,001
1	6,09E-18	0,003	1	0,05	0,000	1	0,10	0,000	1	0,81	0,000	1	0,33	0,002
PRS-CS Scores														
Threshold	***P***	**R^2**	**Threshold**	***P***	**R^2**	**Threshold**	***P***	**R^2**	**Threshold**	***P***	**R^2**	**Threshold**	***P***	**R^2**
1	3,08E-31	0,005	1	1,73E-03	0,001	1	8,09E-01	0,000	1	0,80	0,000	1	0,73	0,000

Note. UKB EUR "White non-British" participants form the UK Biobank, *UKB SAS* "Asian or Asian British" participants form the UK Biobank, *UKB AFR* "Black or Black British" participants from the UK Biobank*, TOP EUR* European ancestry participants from the Thematically Organised Psychosis study, *SAX AFR* African ancestry participants from the Genomics of Schizophrenia in the South African Xhosa People Study.

Appendix 2: Supplementary Note, Figures, and Tables for Chapter 5

A. Supplementary Information

A.1. UK Biobank Cognitive Tests

Fluid Intelligence (*n* = 140,797). Fluid intelligence was measured the UKB Fluid IQ Test, which assesses verbal and numerical reasoning. Verbal reasoning is tested by a series of verbal analogy problems and numerical reasoning is tested with number sequence problems. The participants are given a maximum of 2 minutes to answer 13 multiple-choice questions. The score is taken as the number of correct answers. The UKB fluid intelligence test has acceptable test-retest reliability (Pearson r_{12} = 0.61) (Fawns-Ritchie & Deary, 2020) and internal consistency (Cronbach α = 0.62) (Hagenaars et al., 2016).

Mean reaction time and reaction time variability (*n* = 434,321): The UKB reaction time test is designed to measure processing speed and is based on a Go/NoGo test. During the test, participants were asked to push a button when the 2 cards displayed on screen were matching. The test consisted of 12 trials, 9 of which contained matching cards. Mean reaction time was calculated, in milliseconds, for the trials containing matching cards and reaction time variability was taken as the intraindividual standard deviation of response time for correct responses to trials with matching cards. Both mean reaction time and reaction time variability scores were multiplied by negative one so that higher scores were indicative of better performance. The UKB reaction time test has demonstrated good internal consistency (Cronbach α = 0.85) (Hagenaars et al., 2016), moderate test-retest reliability (Pearson r_{12} = 0.55) (Fawns-Ritchie & Deary, 2020), and good concurrent validity with well-validated tests of reaction time (Fawns-Ritchie & Deary, 2020).

Numeric Memory (*n* = 44,969): The UKB Numeric Reasoning Test is a backward digit span task designed to assess working memory. Participants are shown a two-digit number on the screen, the number disappears, and after a brief pause, the participants are asked to recall the number sequence in reverse order. If the participant makes an error, they are asked to recall a different sequence of the same digit length. The sequence becomes one digit longer every time the participant correctly recalls the digit sequence in reverse order. The test ends when a participant fails to correctly recall two trials of the same digit length or if the participant correctly recalls a 12-digit number. The score is taken as the maximum number of digits correctly remembered in reverse order. The UKB numeric memory test shows reasonably good concurrent validity with validated tests of working memory, and adequate test-retest reliability (Pearson r_{12} = 0.50)(Fawns-Ritchie & Deary, 2020).

Pairs Matching (*n* = 436,853): The UKB Pairs Matching test measures visual memory. Participants are shown pairs of matching cards randomly arranged in a grid on the screen. Participants are then asked to match pairs from memory when the cards are turned face down. Participants complete two trials; one with three card pairs and one with six card pairs. The overall score was the sum of the number of errors made in each trial before all pairs were identified. Scores were multiplied by negative one so that higher scores were indicative of better performance. The UKB pairs matching demonstrated moderate concurrent validity with other tests of visuospatial memory and modest test-retest reliability (Pearson r_{12} = 0.41) (Fawns-Ritchie & Deary, 2020).

Prospective Memory (n = 144,031): The UKB Prospective Memory is designed to assess prospective memory, the ability to remember to perform intended actions in future (Hudson

et al., 2011). The participants were asked to remember instructions for a future task at the beginning of the cognitive test battery. The participants were given a score of 0 or 1 based on whether or not they correctly remembered the instructions and completed the task on the first attempt. The test-retest reliability of UKB Prospective Memory was moderate (Pearson r_{12} = 0.45) (Fawns-Ritchie & Deary, 2020).

Matrix Pattern Completion (*n* = 28,922): The UKB Matrix Pattern Completion measures non-verbal reasoning and is adapted from the COGNITO Matrices Test (Ritchie et al., 2014). Participants were asked to complete 15 puzzles that ranged in difficulty. For each puzzle, the participant was shown a matrix design with a missing piece, and they were asked to use logic to identify the missing piece from 6-8 options. The test score was the number of correctly solved puzzles in 3 minutes. The UKB matrices showed good concurrent validity with the COGNITO Matrices Test and moderate test-retest reliability (Pearson r_{12} = 0.45)(Fawns-Ritchie & Deary, 2020).

Paired Associate Learning (*n* = 34,364): The UKB Paired Associate Learning (PAL) test is based on a version of Paired Associate Learning test from Test the Nation (Cooper, 2003) and is designed to assess verbal declarative memory. During the learning phase of the test, participants were shown 12 word pairs and were instructed to try to remember the word pairs as they would be asked to recall them at a later stage. Next, the participants completed the UKB matrices. Upon completion of the UKB matrices, participants resumed the UKB PAL. Participants were shown one word from a word pair (the target word) and were asked to select the word that completed the pair from a list of four options. Participants completed 10 trials

and the score was the correct trials. The UKB PAL has acceptable test-retest reliability (Pearson r_{12} = 0.45) (Fawns-Ritchie & Deary, 2020) and good concurrent validity.

Symbol Digit Substitution (*n* = 28,949): UKB Symbol Digit measures processing speed. During the test, participants were shown a key, which paired symbols with numbers. Participants were instructed to use the key to pair a row of symbols with the corresponding number. The score was the number of correct symbol-digit matches made in 60 seconds. The psychometric properties of the UKB Symbol Digit are good (Fawns-Ritchie & Deary, 2020).

Tower Rearranging (*n* = 28,688): The UKB Tower Test was adapted from the One-touch Tower of London test (Shallice, 1982) and is designed to assess planning ability, an aspect of executive function. During each trial of the task, participants were shown a display (display A) of 3 different coloured hoops arranged on 3 pegs. Beneath display A was display B, which also showed 3 different coloured hoops arranged on 3 pegs however, the coloured hoops were arranged in a different order to those shown in display A. For each trial, participants were asked the minimum number of moves required to change display A into display B. The score was the number of correct trials completed in 3 minutes.

Trail Making Test (Part A *n* = 28,899; Part B *n* = 28,156): The UKB Trail Making Test (UKB TMT) is an adapted version of the Halstead-Reitan Trail Making Test (Reitan & Wolfson, 1985), a measure of executive function. During part A of the test, participants were shown the numbers 1-25 pseudo-randomly arranged on the computer screen. Participants were instructed to touch the numbers in ascending order. During part B, the numbers 1-13 and letters A-L were displayed pseudo-randomly on the screen. Participants were instructed to

alternate between touching the numbers in ascending order and the letters in alphabetical order. The score was the sum of the time, in deciseconds, taken to complete each part. For this analysis, scores were multiplied by negative one so that higher scores were indicative of better performance.

A.2. References

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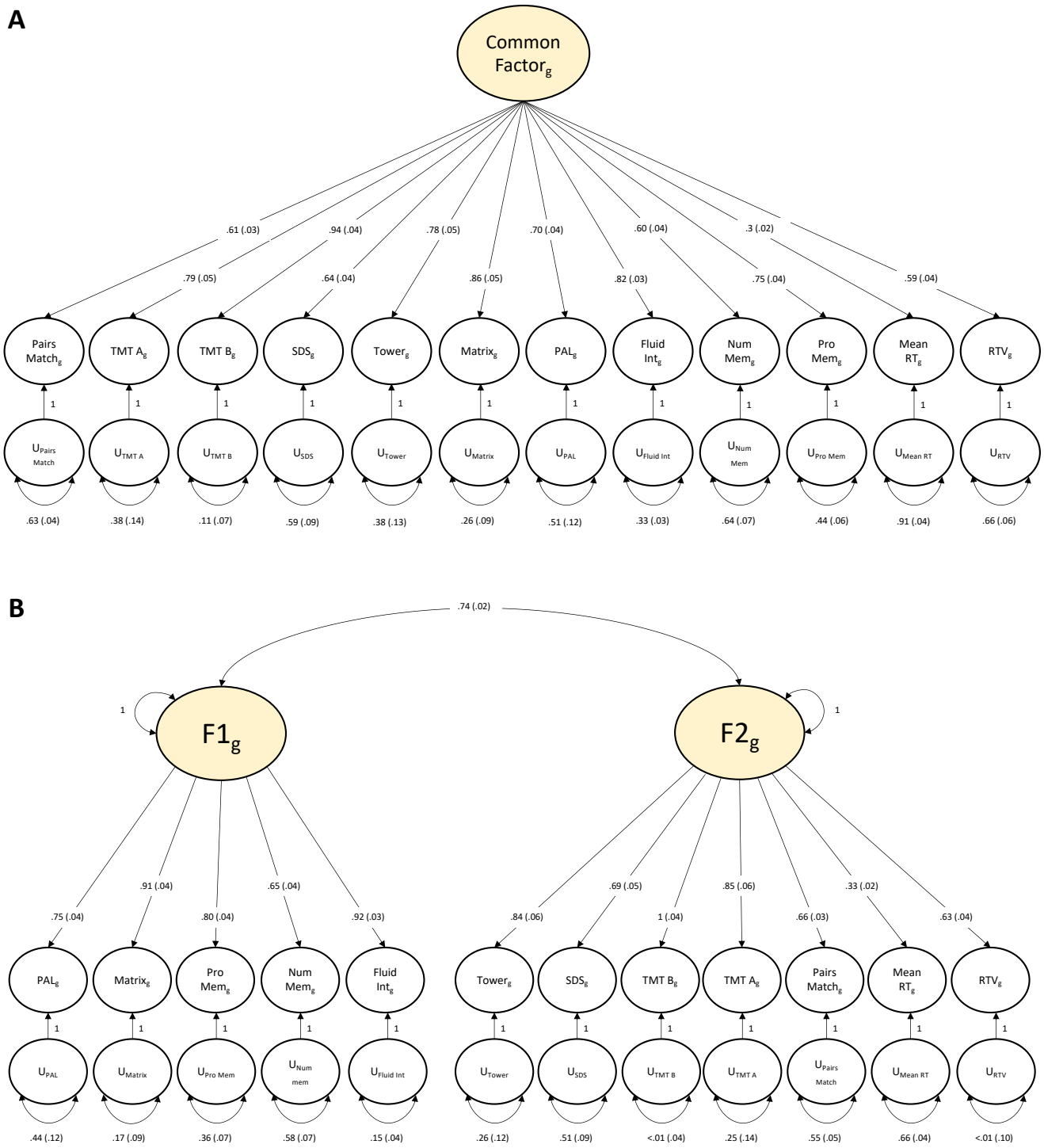
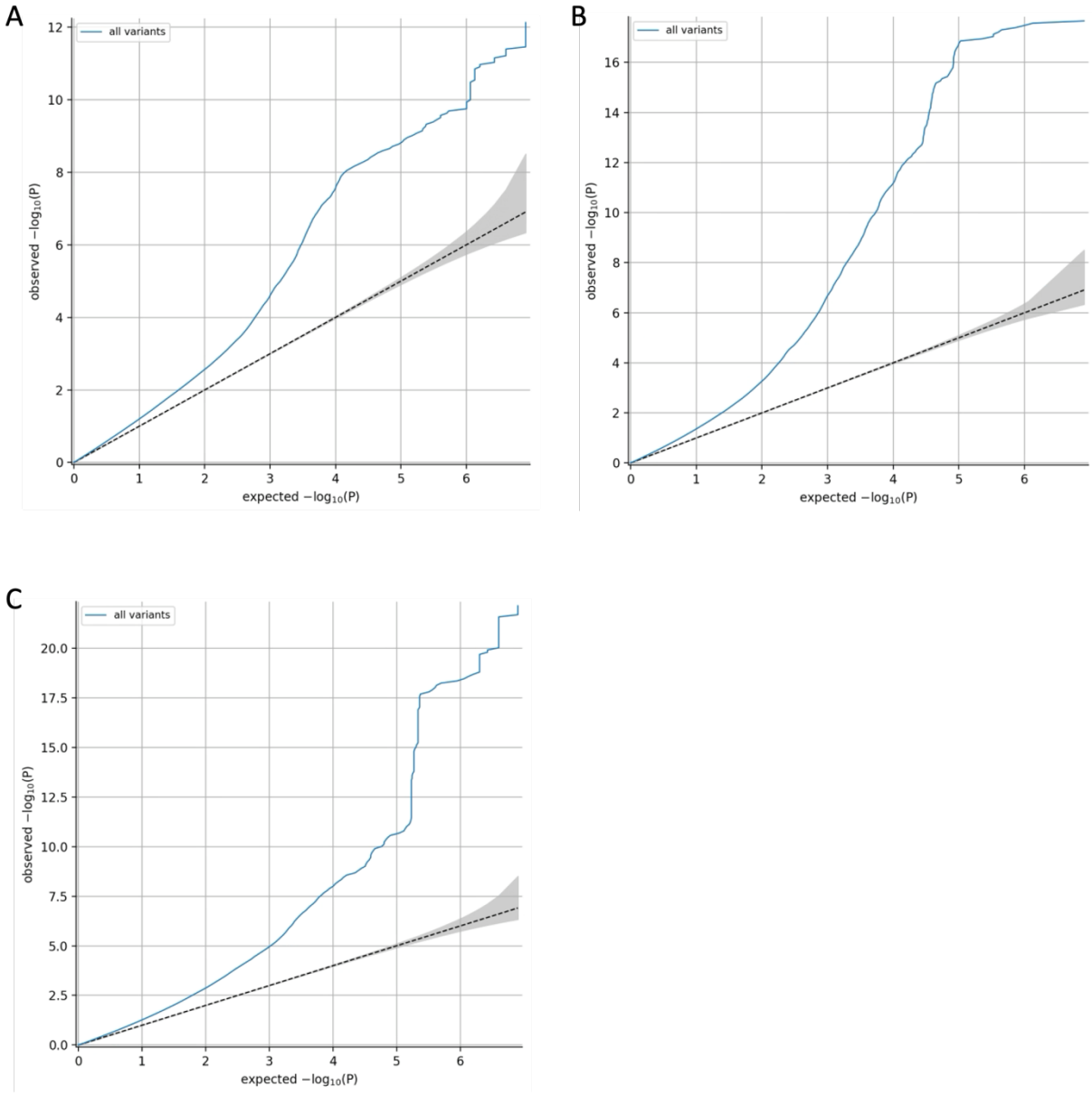
B. Supplementary Figures



Supplementary Figure 5. 1: Standardized Genetic Factor Solutions for the Covariance Structure of 12 UKB Cognitive Traits

(**A**) The path diagram for the common factor model. (**B**) The path diagram for the correlated two factor model. Circles represent latent variables that are inferred from the data. Single-

headed arrows depict regression relationships with the arrows pointing from the independent variables to the dependent variables. Two-headed arrows represent covariance relationships between variables or the residual variance of a variable if the arrow connects the variable to itself. Standard errors of the estimates are in parenthesis.



Supplementary Figure 5. 2: Quantile-quantile Plots

Quantile-quantile plot of expected under null (no association, x axis) versus observed (y axis) -log10 p-values for the multivariate GWAS of latent cognitive factor 1 (**A**), factor 2 (**B**), and factor 3 (**C**).

C. Supplementary Tables

Supplementary Table 5. 1: Summary of Univariate GWAS Results for the Twelve Cognitive Traits

Trait	GWS Loci	λ_{GC}	LD Intercept	h^2 (SE)
Fluid Intelligence (Fluid Int)	67	1.50	1.03	0.22 (0.009)
Mean Reaction Time (Mean RT)	89	1.56	1.04	0.08 (0.003)
Numeric Memory (Num Mem)	5	1.15	1.01	0.18 (0.014)
Pairs Matching (Pairs Match)	25	1.30	1.01	0.04 (0.002)
Prospective Memory (Pro Mem)	5	1.16	1.02	0.06 (0.004)
Matrix Reasoning (Matrix)	5	1.09	1.00	0.16 (0.019)
Pairs Associated Learning (PAL)	0	1.08	1.00	0.12 (0.015)
Symbol Digit Substitution (SDS)	2	1.09	1.00	0.15 (0.018)
Tower Rearranging (Tower)	0	1.07	1.01	0.11 (0.018)
Trail Making Test - Part A (TMT_A)	2	1.06	1.00	0.017 (0.10)
Trail Making Test - Part B (TMT_B)	0	1.10	1.01	0.19 (0.018)
Reaction Time Variability (RTV)	7	1.07	1.00	0.03 (0.002)

Note. $\boldsymbol{\lambda_{GC}}$ genomic inflation factor, *GWS* genome-wide significant, h^2_{SNP} single nucleotide polymorphism based heritability, *LD* linkage disequilibrium, *SE* standard error

Supplementary Table 5. 2: Model Fit Statistics for One-, Two-, and Three-Factor Genomic Structural Equation Models

Model	χ2 statistic	df	AIC	CFI	SRMR
Common factor	2106.75	54	2154.75	0.71	0.12
Correlated two-factor model	1578.34	53	1628.34	0.78	0.09
Correlated three-factor model	320.72	49	378.72	0.96	0.07

Note. AIC Akaike's Information Criterion, χ2 chi-squared statistic, *CFI* Comparative Fit Index, *df* degrees of freedom, *SRMR* standardised root mean squared residual

Supplementary Table 5. 3: Genetic Correlations and Percentage of Concordant Shared Variants Between Each Latent Cognitive Factor and Schizophrenia

Cognitive Factor	rg (SE)	*P* for rg	Concordant Shared Variants (%)
Factor 1 (visuospatial processing)	-0.38 (0.03)	9.01E-52	37
Factor 2 (verbal analytic reasoning)	-0.26 (0.02)	1.42E-33	41
Factor 3 (decision/reaction time)	-0.26 (0.02)	3.54E-38	40

Note. *rg* genetic correlation

Supplementary Table 5. 4: Summary of LAVA Results

Phenotype Pair	Number of nominally significant correlated regions		Number of significantly correlated regions after Bonferroni correction	
	Positive	Negative	Positive	Negative
Factor 1 & SCZ	43	106	0	6
Factor 2 & SCZ	60	178	2	19
Factor 3 & SCZ	53	117	0	8

Note. *SCZ* schizophrenia

Supplementary Table 5. 5: LAVA Results for Loci with Significant Local Genetic Correlations Between a Latent Cognitive Factor and Schizophrenia

Latent Cognitive Factor	Locus	CHR	Start	Stop	SNPs	PCs	Rho	Rho CI Lower	Rho CI Upper	R2	P	h2 SCZ	P for h2 SCZ	h2 Cognitive Factor	P for h2 Cognitive Factor
1	30	1	30405183	31639217	3127	308	-0.63	-0.98	-0.34	0.39	3.99E-05	1.82E-03	9.86E-15	1.98E-04	2.76E-06
1	803	5	30416067	31679464	3083	303	-0.70	-1.00	-0.38	0.48	6.52E-05	1.09E-03	4.16E-07	2.23E-04	1.84E-07
1	952	6	27261036	28666364	2823	123	-0.63	-0.94	-0.39	0.40	5.95E-06	2.68E-03	4.51E-39	1.32E-04	2.98E-06
1	958	6	31106494	31250556	1650	39	-0.91	-1.00	-0.67	0.84	3.09E-07	1.49E-03	3.25E-27	7.72E-05	1.12E-05
1	959	6	31250557	31320268	1236	37	-1.0	-1.00	-0.80	1.00	1.20E-08	1.56E-03	3.43E-29	7.51E-05	1.27E-05
1	965	6	32586785	32629239	548	133	-0.62	-0.81	-0.45	0.38	3.42E-09	3.78E-03	8.26E-60	2.38E-04	4.64E-13
2	158	1	205009624	205917548	2221	248	-0.82	-1.00	-0.49	0.68	6.90E-06	9.47E-04	1.34E-06	7.85E-04	3.85E-07
2	278	2	72160303	73544290	2022	227	-0.62	-0.94	-0.35	0.38	4.03E-05	1.31E-03	8.84E-11	9.14E-04	2.78E-09
2	444	3	23426045	24270189	1888	222	-0.81	-1.00	-0.55	0.66	2.41E-07	1.03E-03	5.24E-08	1.04E-03	2.68E-11
2	464	3	47588462	50387742	2761	189	0.78	0.49	1.00	0.60	3.24E-06	9.10E-04	4.00E-07	9.28E-04	1.56E-10
2	483	3	71223282	72334704	2675	350	-0.52	-0.77	-0.30	0.27	1.72E-05	1.58E-03	4.91E-11	1.78E-03	6.19E-19
2	577	3	176931164	178110322	2487	284	-0.75	-1.00	-0.44	0.55	9.81E-06	1.25E-03	4.78E-09	8.16E-04	6.00E-07
2	950	6	25684630	26396200	1802	126	-0.87	-1.00	-0.64	0.76	6.42E-09	2.19E-03	9.39E-30	5.09E-04	6.08E-06
2	951	6	26396201	27261035	1437	93	-0.76	-1.00	-0.53	0.58	1.08E-07	2.33E-03	9.28E-36	5.22E-04	3.58E-07
2	952	6	27261036	28666364	2823	123	-0.51	-0.75	-0.29	0.26	3.31E-05	2.68E-03	4.51E-39	7.33E-04	1.17E-09
2	953	6	28666365	29529755	2414	90	-0.58	-0.81	-0.35	0.34	6.28E-06	2.42E-03	4.75E-37	6.54E-04	9.78E-10
2	954	6	29529756	29833843	2402	54	-0.62	-0.87	-0.38	0.38	1.46E-05	1.81E-03	1.80E-31	5.20E-04	3.07E-09
2	955	6	29833844	30070717	1896	44	-0.83	-1.00	-0.64	0.68	3.81E-09	1.76E-03	2.43E-32	5.39E-04	1.61E-10
2	956	6	30070718	30715006	2499	92	-0.69	-0.92	-0.45	0.47	2.37E-07	2.01E-03	6.18E-27	6.96E-04	1.87E-10
2	977	6	42103739	43770626	3069	295	-0.85	-1.00	-0.58	0.72	2.45E-08	1.88E-03	1.03E-15	7.69E-04	2.84E-06

Latent Cognitive Factor	Locus	CHR	Start	Stop	SNPs	PCs	Rho	Rho CI Lower	Rho CI Upper	R2	P	h2 SCZ	P for h2 SCZ	h2 Cognitive Factor	P for h2 Cognitive Factor
2	1389	9	14244748	14902924	1871	314	-0.71	-1.00	-0.36	0.51	1.55E-04	9.69E-04	4.72E-06	8.11E-04	1.75E-06
2	1522	10	33655459	35178224	3304	313	-0.59	-0.89	-0.33	0.35	2.06E-05	1.77E-03	3.15E-14	1.02E-03	6.96E-09
2	1731	11	126304241	127306871	2676	302	-0.63	-1.00	-0.33	0.40	9.96E-05	1.47E-03	9.42E-11	7.88E-04	2.16E-06
2	1735	11	130500784	131424361	2343	332	-0.58	-0.91	-0.31	0.33	5.97E-05	2.13E-03	9.06E-18	8.33E-04	1.68E-06
2	1812	12	77800464	79315178	3425	308	0.58	0.29	0.92	0.34	1.28E-04	1.52E-03	3.27E-11	9.24E-04	7.69E-08
2	1963	14	29029225	30831154	3071	317	-0.52	-0.74	-0.32	0.27	2.89E-06	2.28E-03	2.67E-20	1.47E-03	4.34E-15
2	2478	22	33501726	34361897	2316	281	-0.91	-1.00	-0.61	0.82	7.21E-08	1.46E-03	2.87E-11	7.18E-04	6.79E-06
3	1203	7	121946053	123859746	3642	258	-0.67	-1.00	-0.35	0.45	1.46E-04	9.67E-04	8.37E-07	2.23E-04	1.64E-07
3	1657	11	45019560	46316005	2610	255	-0.55	-0.79	-0.34	0.30	2.83E-06	1.35E-03	1.37E-10	5.45E-04	1.70E-27
3	1658	11	46316006	48066366	2071	170	-0.63	-1.00	-0.32	0.40	2.71E-04	1.32E-03	5.47E-13	1.45E-04	1.90E-05
3	1754	12	13559528	14656849	2775	263	-0.71	-1.00	-0.37	0.50	1.68E-04	8.27E-04	2.16E-05	2.34E-04	5.94E-08
3	1899	13	58245844	59751795	3171	184	-0.64	-1.00	-0.33	0.41	1.66E-04	7.96E-04	2.04E-06	2.48E-04	1.36E-10
3	2054	15	46884072	47693316	1940	123	-0.76	-1.00	-0.41	0.58	1.36E-04	7.39E-04	7.34E-07	1.43E-04	2.28E-06
3	2235	17	78438333	79333774	2861	274	-0.76	-1.00	-0.45	0.58	9.07E-06	1.28E-03	1.15E-09	1.98E-04	3.38E-06
3	2478	22	33501726	34361897	2316	281	-0.54	-0.82	-0.27	0.29	1.28E-04	1.46E-03	2.87E-11	3.01E-04	6.81E-11

Note. Chr chromosome, *CI* confidence interval, h_2 heritability, *SNP* single nucleotide polymorphism

Supplementary Table 5. 6: Genes that Map to Unique Loci Jointly Associated with Cognitive Factor 1 and Schizophrenia

Locus	Chr	Start	Stop	Genes
3	1	103210618	103399207	*RP5-936J12.1; COL11A1*
6	2	10915957	10988762	*RNU7-176P; PDIA6; AC092687.4; ATP6V1C2*
9	2	37454285	37578303	*AC007391.2; RNU6-939P; CEBPZ; NDUFAF7; QPCT; PRKD3*
14	2	208229500	208329196	*AC007879.5*
15	3	17219136	17885531	*AC090960.1; AC140076.1; U7; AC104451.2; TBC1D5*
18	3	123961087	124047094	*KALRN*
19	3	170627908	170744815	*KLF7P1; RNU1-70P; SLC2A2*
22	4	5191067	5232752	*STK32B*
24	4	80186914	80255322	*LINC01088; NAA11*
25	4	129723380	130058979	*RP11-392L5.2; ZSWIM5P3; JADE1; SCLT1; C4orf33*
27	4	170275955	170646968	*CLCN3; NEK1*
28	4	176835889	176919065	*RP11-598O12.1; GPM6A*
29	5	152869623	152895508	*GRIA1; RN7SL339P; RP11-117L6.1; SNORA70; RP11-546B8.5; MIR3912; NPM1; FGF18*
30	5	170776746	170848124	*RN7SL339P; RP11-117L6.1; SNORA70; RP11-546B8.5; MIR3912; NPM1; FGF18*
31	5	178988607	179060529	*PRDX2P3; RP11-1379J22.2; RUFY1; HNRNPH1*
37	6	152772493	152835820	*SYNE1*
39	7	78316879	78414989	*MAGI2*
42	7	110034962	110109897	*AC003088.1*
44	7	131533768	131567263	*AC008085.1*
46	7	137039669	137085250	*DGKI*
51	9	100991429	101060141	*RP11-270F18.2; TBC1D2; GABBR2*
52	9	124681857	124714491	*TTLL11-IT1; TTLL11*
53	10	18755988	18782777	*CACNB2*
54	10	62085589	62175060	*ANK3*

Locus	Chr	Start	Stop	Genes
58	11	113802600	113827103	*HTR3B*
62	12	57622370	57682956	*SHMT2; NDUFA4L2; STAC3; R3HDM2; RP11-123K3.4*
67	13	38291966	38345920	*TRPC4*
68	13	66977226	67131103	*PCDH9*
70	13	97128573	97376923	*AMMECR1LP1; HS6ST3*
72	14	98603850	98670849	*RP11-61O1.2; RP11-61O1.1*
73	14	99700079	99751267	*AL109767.1; BCL11B*
76	15	63444686	63598430	*RAB8B; RPS27L; APH1B*
79	16	29923509	30380486	*CTD-2574D22.4; CTD-2574D22.2; HIRIP3; C16orf92; PPP4C; YPEL3; RP11-455F5.4; GDPD3; BOLA2B; SLX1A; RP11-347C12.9; RP11-347C12.3; RP11-347C12.8; snoU13; RP11-347C12.10; CD2BP2; ASPHD1; KCTD13; TMEM219; TAOK2; DOC2A; FAM57B; ALDOA; RP11-455F5.3; TBX6; MAPK3; RP11-455F5.5; SLX1A-SULT1A3; CORO1A; SULT1A3; RP11-347C12.1; TBC1D10B; INO80E;RP11-347C12.2*
80	17	28697678	28893678	*RP11-218M11.3; RP11-218M11.1; CPD; ALOX12P1; RP11-271K11.1; RP11-218M11.6; TBC1D29; GOSR1*
83	19	2106558	2249634	*AC004490.1; MIR1227; PLEKHJ1; AMH; AP3D1; SF3A2; DOT1L*
85	19	18575192	18589943	*ELL*
89	20	48090778	48132580	*KCNB1; PTGIS*
90	21	37645998	37667579	*SRSF9P1; DOPEY2*

Supplementary Table 5. 7: Genes that Map to Unique Loci Jointly Associated with Cognitive Factor 2 and Schizophrenia

Locus	Chr	Start	Stop	Genes
1	1	22353326	22470115	*LINC00339; CDC42-IT1; RP1-224A6.8; RP1-224A6.9; WNT4; CDC42*
2	1	41832296	41851415	*RP11-399E6.4; FOXO6*
4	1	57199972	57211399	*C1orf168*
6	1	92664965	93035020	*RP4-775D17.1; ACTBP12; AL451010.1; RN7SL824P; C1orf146; GLMN; GFI1; RPAP2; EVI5*
7	1	96307777	96972973	*AC092812.1; RNU1-130P; RP4-736I12.1; UBE2WP1; EEF1A1P11; RP5-898J17.1; RP11-147C23.1*
9	1	151597093	151723030	*RNU6-1062P; RP11-98D18.1; RNU6-662P; CELF3; RIIAD1; AL589765.1; SNX27*
10	1	153758561	154227119	*RP11-216N14.5; RP11-216N14.7; RP11-759F5.1; RP11-422P24.10; SLC39A1; RP11-422P24.11; JTB; RAB13; RP11-422P24.9; U3; RPS27; RNU6-179P; RPS7P2; MIR5698; RN7SL431P; MIR190B; AL590431.1; DENND4B; CRTC2; CREB3L4; C1orf189; C1orf43; UBAP2L; GATAD2B; NUP210L; TPM3*
11	1	154630334	154691575	*KCNN3*
13	1	173370334	174572982	*RP11-360D2.1; snoU13; RP11-360D2.2; RN7SKP160; Y_RNA; GAS5-AS1; SNORD78; RNA5SP67; RNA5SP68; RP11-160H22.3; RPL30P1; snoU13; AL022400.1; RP4-809F4.1; GPR52; PRDX6; ANKRD45; KLHL20; CENPL; GAS5; ZBTB37; SERPINC1; RC3H1-IT1; RP11-160H22.5; RP11-296O14.3; RP3-436N22.3; SLC9C2; DARS2; RC3H1; RABGAP1L*
15	1	177237532	177419629	*RP1-35C21.1; RP1-35C21.2; BRINP2*
16	1	208034954	208038968	*C1orf132*
18	2	22430794	22606275	*AC099799.1; RNA5SP87; AC068490.2; AC096570.2*
20	2	25323082	25387181	*RP11-509E16.1; POMC; EFR3B*
21	2	26961165	27345484	*CDKN2AIPNLP2; AGBL5-AS1; RP11-503P10.1; AGBL5-IT1; RP11-195B17.1; OST4; EMILIN1; AC013472.4; AC013472.3; MAPRE3; AGBL5; KHK; CGREF1; SLC35F6; CENPA; DPYSL5; TMEM214;*
24	2	56610678	56899310	*RP11-482H16.1; CCDC85A*
26	2	60610410	60727416	*RNU1-32P; MIR4432; AC009970.1; AC007381.2; BCL11A;*
27	2	68354897	68507833	*RP11-474G23.2; AC017083.1; RP11-474G23.3; AC017083.3; WDR92; PNO1; RP11-474G23.1; PPP3R1;*
31	2	79910115	79932429	*CTNNA2*
32	2	97532848	97579507	*SEMA4C; FAM178B*
34	2	142519783	142572950	*LRP1B*

Locus	Chr	Start	Stop	Genes
35	2	144042332	144264450	*AC096558.1; RP11-570L15.2; ARHGAP15;*
36	2	144946334	145121339	*GTDC1*
38	2	156835298	156933105	*AC073551.1; AC093375.1*
39	2	161994382	162101261	*AC009299.2; AC009299.3; AC009313.1; TANK*
41	2	164889133	164930382	*AC092684.1*
42	2	173929606	174072081	*MLK7-AS1; MLTK*
43	2	175170618	175175807	*HNRNPA1P39*
46	2	198148190	198954774	*AC010746.3; NPM1P46; SNORA4; RNU6-1029P; HSPE1; AC020550.7; MARS2; ANKRD44-IT1; SF3B1; COQ10B; HSPD1; HSPE1-MOB4; MOB4; BOLL; ANKRD44; RFTN2; AC011997.1; PLCL1*
49	2	203499511	203632793	*FAM117B*
50	2	215248491	215406008	*VWC2L-IT1; AC107218.3; VWC2L; SPAG16*
52	2	228243904	228455593	*MIR5703; TM4SF20; AGFG1*
55	3	16712665	17151217	*AC091493.2; AC091493.1; MIR3714; PLCL2-AS1; PLCL2*
56	3	18017415	18392551	*AC132807.1; SATB1; TBC1D5*
58	3	36859704	36948417	*AC011816.1; TRANK1;*
59	3	48381147	50910004	*RN7SL321P; RP11-24C3.2; TMA7; TREX1; AC104448.1; UCN2; MIR711; TMEM89; SLC26A6; MIR4793; RP11-148G20.1; RP11-572O6.1; PRKAR2A-AS1; RP13-131K19.2; RP13-131K19.7; WDR6; MIR425; MIR191; RP13-131K19.6; NDUFAF3; IMPDH2; RN7SL182P; KLHDC8B; RP11-3B7.7; RP11-3B7.1; Y_RNA; MIR4271; C3orf62; GPX1; RHOA-IT1; NICN1-AS1; TCTA; AMT; RNA5SP130; BSN-AS2; BSN-AS1; AC099668.5APEH; COX6CP14; RP13-1056D16.2; CDHR4; MIR5193; AC139451.1; FAM212A; UBA7; RN7SL217P; ACTBP13; CTD-2330K9.3; MIR566; U73169.1; SEMA3B-AS1; SEMA3B; LSMEM2; IFRD2; NAT6; HYAL2; RASSF1; NPRL2; CYB561D2TMEM115; XXcos-LUCA11.4;RNA5SP131; C3orf18; CISH;MIR4787; RP11-804H8.5;RP11-646D13.1;ZNF652P1; FBXW12;PLXNB1;CCDC51; SHISA5;PFKFB4; UQCRC1; CELSR3; NCKIPSD; PRKAR2A; SLC25A20; ARIH2OS; P4HTM; DALRD3; QRICH1; QARS;RP11-694I15.7; LAMB2; CCDC71; C3orf84; USP4; NICN1; MST1; RNF123; AMIGO3; GMPPB; TRAIP; CAMKV; MON1A; RBM5; RP11-493K19.3; GNAT1; GNAI2; SLC38A3; U73166.2; HYAL1; TUSC2; ZMYND10; XXcos-LUCA11.5; ZMYND10-AS1; HEMK1; MAPKAPK3; RP11-804H8.6; RP13-131K19.1; ATRIP; COL7A1; IP6K2; ARIH2; USP19; SEMA3F; CTD-2330K9.2; RHOA;DAG1; BSN; IP6K1; MST1R; RBM6; CACNA2D2; CCDC36; DOCK3; HYAL3*
62	3	71481191	71684845	*MIR1284; FOXP1-IT1; RP11-154H23.3; FOXP1*
63	3	105226245	105237260	*ALCAM*

Locus	Chr	Start	Stop	Genes
68	3	185399915	185445144	*C3orf65; IGF2BP2*
74	4	102195415	103388441	*MIR1255A; AP001816.1; RNU6-462P; MTND5P5; RN7SL728P; RP11-498M5.2; RP11-499E18.1; AF213884.1; PPP3CA; SLC39A8; BANK1*
75	4	103640757	104129141	*LRRC37A15P; KRT8P46; RP11-10L12.1; RP11-10L12.2; RNU7-151P; snoU13; PABPC1P7; ACTR3BP4; RP11-10L12.4; UBE2D3; SLC9B2; BDH2; MANBA; CENPE; CISD2; SLC9B1*
76	4	106033258	106467767	*AC004069.2; TET2-AS1; RN7SL89P; RNU6-553P; EEF1A1P9; AC004066.2; ATP5EP1; AC004066.3; TET2; PPA2; RP11-556I14.1*
78	4	139939449	140402076	*RNU6-531P; RN7SL382P; PPP1R14BP3; RN7SL311P; Y_RNA; RNU6-506P; RNU6-1074P; RNU6-1214P; RP11-83A24.1; ACA64; CCRN4L; MGARP; NDUFC1; RP11-83A24.2; RAB33B; ELF2; NAA15*
79	4	140753102	140809005	*MAML3*
80	4	156131407	156308551	*NPY2R; RP11-27G13.1; YWHAEP4; RP11-27G13.4; RP11-27G13.5; MAP9; AC097467.2*
82	4	176922277	176973535	*MARK2P4; AC110794.1; GPM6A*
83	5	6600491	6626673	*NSUN2*
84	5	12784340	12988181	*RP11-419C19.3; RP11-419C19.1; RP11-419C19.2; CT49*
85	5	81571845	81648417	*RPS23; ATG10; ATP6AP1L*
86	5	88215593	88223420	*MEF2C-AS1*
87	5	89252601	89407917	*MIR3660*
88	5	92376459	92586991	*CTD-2091N23.1*
89	5	103703059	104092550	*RP11-6N13.1*
90	5	106220962	106244066	*CTC-254B4.1*
91	5	106788038	106796207	*EFNA5*
92	5	107145323	107256585	*RN7SKP122; FBXL17*
93	5	110982397	111034953	*STARD4-AS1; NREP*
94	5	139729151	140346468	*CTC-329D1.3; SLC4A9; RNU4-14P; SNORD45; EIF4EBP3; SLC35A4; SNORA27; HAUS1P1; RP11-515C16.1; CD14; MIR3655; NDUFA2; TMCO6; HARS2; VTRNA1-1; VTRNA1-2; VTRNA1-3;RP11-515C16.7; AC005609.2; PCDHA14; AC005609.1; CTC-329D1.2; SRA1; APBB3; IK; WDR55; DND1; HARS; ZMAT2; ANKHD1; ANKHD1-EIF4EBP3; PCDHA1; PCDHA2; PCDHA3; PCDHA4; PCDHA5; PCDHA6; PCDHA7; PCDHA8; PCDHA9; PCDHA10; PCDHA11; PCDHA12; PCDHA13; PCDHAC1; PCDHAC2*
95	5	151874411	152096515	*CTC-550M4.1; AC091969.1*
101	6	20630159	20666457	*CDKAL1*

Locus	Chr	Start	Stop	Genes
103	6	33198770	33442692	*HTATSF1P; XXbac-BPG157A10.21; HCG25; B3GALT4; WDR46; ZBTB22; MYL8P; LYPLA2P1; RPL35AP4; RPL12P1; PHF1; CUTA; MIR5004; VPS52; RPS18; PFDN6; RGL2; TAPBP; KIFC1; SYNGAP1 DAXX ZBTB9*
105	6	78305073	79011375	*SNORD112; MEI4*
106	6	97374849	97429208	*KLHL32*
107	6	98421990	98591622	*MIR2113; RP11-436D23.1*
109	6	114679176	114775668	*RP3-399L15.3*
110	6	125007326	125076164	*NKAIN2*
115	7	3953157	3996924	*SDK1*
117	7	39090683	39245781	*POU6F2*
118	7	44591276	44935702	*TMED4; RP11-52M17.1; AC004854.4; MIR4657; DDX56; ZMIZ2; RP4-673M15.1; PPIA; H2AFV; PURB; AC013436.6; OGDH*
119	7	68791968	69837848	*RP11-666G4.2; RP11-666G4.1; RNU6-229P; Y_RNA; RN7SL371P; RP5-942I16.1; RP11-3P22.2; AUTS2*
120	7	71437061	71872935	*ABCF2P2; CALN1*
121	7	87141813	87564497	*HNRNPA1P9; snoU13; SLC25A40; DBF4; ABCB1; RUNDC3B; ADAM22*
124	7	114856050	114922151	*AC068610.5*
125	7	121938745	121950965	*FEZF1-AS1; FEZF1*
128	7	128373608	128419388	*OPN1SW; RN7SL81P; CALU*
130	7	134471210	134509484	*CALD1*
131	7	137095229	137132859	*DGKI*
132	7	140809204	140870388	*TMEM178B*
133	7	154724653	154897104	*RP11-5C23.1; RP11-5C23.2; HTR5A; PAXIP1-AS2; PAXIP1; HTR5A-AS1; PAXIP1-AS1*
134	7	157467231	157536448	*AC006003.3; PTPRN2*
135	8	4177790	4210746	*CSMD1*
137	8	12507535	12615440	*OR7E8P; OR7E15P; OR7E10P; MIR5692A1; MIR3926-2; RP11-303G3.10; LONRF1*
139	8	33799775	33980486	*RP1-273G13.2; RP1-273G13.3; RP11-317N12.1*
140	8	55525484	55761124	*RP11-550I15.1; RP1; RP11-56A10.1*
142	8	69179165	69206699	*RPL31P40*

Locus	Chr	Start	Stop	Genes
143	8	84287972	84453966	*RP11-51M18.1*
145	8	106287971	106381940	*RP11-273P3.1; ZFPM2; RP11-127H5.1*
146	8	130853446	130985863	*RP11-473O4.5; RP11-473O4.1; SNORA25; RP11-473O4.4; RP11-473O4.3; FAM49B*
150	9	6305621	6411838	*TPD52L3*
152	9	22615603	22747408	*RP11-399D6.2*
153	9	23692124	23718620	*ELAVL2*
154	9	34852610	35098008	*FAM205CP; GLULP4; YWHAZP6; SYF2P2; FLJ00273; RN7SL338P; RP11-182N22.8; KIAA1045; C9orf131; VCP; FANCG; PIGO; DNAJB5*
155	9	36302387	36319728	*HMGB3P24; CLTA*
156	9	72036072	72166573	*RP11-548B3.3; RP11-470P21.2; APBA1*
157	9	84521380	85129970	*SPATA31D5P; RP11-383M4.2; SPATA31D4; SPATA31D3; SPATA31D2P; SPATA31B1; DDX10P2; RP11-388B24.4; RP11-15B24.1; RP11-15B24.2; RP11-15B24.3; RP11-15B24.4; RP11-383M4.6; SPATA31D1; RP11-15B24.5*
160	9	130335417	130480322	*MIR3911; C9orf117; PTRH1; TTC16; FAM129B; STXBP1*
161	9	131838820	131956432	*DOLPP1; RP11-247A12.1; AL158151.2; RP11-247A12.7; RP11-247A12.8; RP11-247A12.2; PPP2R4; IER5L; CRAT*
162	9	136924743	136942560	*BRD3*
166	10	53813180	53822301	*PRKG1*
169	10	106399998	106768514	*SORCS3-AS1; SORCS3*
170	10	107289061	107567415	*RNU6-463P; RP11-45P22.2; YWHAZP5*
171	11	17019361	17423407	*AC116533.3; AC116533.2; AC116533.1; SNORD14A; SNORD14B; RPS13; RNU6-593P; CTD-3236F5.1; RP11-452G18.1; RP11-452G18.2; RP1-239B22.5; KCNJ11; NCR3LG1; OR7E14P; PLEKHA7; PIK3C2A; NUCB2; ABCC8*
172	11	28591167	28741185	*RP11-960D24.1; RP11-115J23.1*
173	11	45915596	45945969	*RP11-618K13.2; C11orf94; PEX16; GYLTL1B; MAPK8IP1*
176	11	63852715	64009879	*RP11-21A7A.4; RP11-21A7A.3; TRPT1; RP11-783K16.14; DNAJC4; VEGFB; FKBP2; FLRT1; FERMT3; NUDT22; MACROD1; RP11-21A7A.2; STIP1*
181	11	124276496	124303201	*OR8B4*
184	11	134209428	134209565	*GLB1L2*
185	12	1786311	1899714	*RP11-288K12.1; RPS4XP14; ADIPOR2*

Locus	Chr	Start	Stop	Genes
187	12	6842958	6867350	*RP4-761J14.10; MLF2*
188	12	29905250	29940392	*TMTC1*
190	12	53605343	54072180	*MFSD5; RP11-680A11.5; C12orf10; RP11-793H13.11; TARBP2; NPFF; RP11-793H13.3; RP11-972K6.1; ESPL1; PFDN5; AAAS; SP7; RP11-793H13.8; SP1; AMHR2; PRR13; MAP3K12; ATP5G2; RARG; PCBP2; RP11-793H13.10; ATF7*
191	12	57246940	57490100	*RP11-74M13.3; SNORA48; RDH16; GPR182; HBCBP; RP11-474N8.5; NAB2; RP11-74M13.4; SDR9C7; ZBTB39; MYO1A; TMEM194A; STAT6; TAC3*
192	12	70361685	70392995	*RP11-611E13.2*
193	12	72223302	72322443	*RP11-2H8.3; MRS2P2; TBC1D15*
195	12	82075293	82139722	*PPFIA2*
197	12	108595295	108629780	*WSCD2*
201	13	51067233	51121893	*RP11-175B12.2; DLEU1*
202	13	56438042	57537565	*SPATA2P1; snoU13; RN7SKP6; HNF4GP1*
204	13	63410741	63787601	*LINC00376*
206	14	29309810	29662737	*Y_RNA; CTD-2384A14.2; RNU6-864P; RP11-30H9.1; RP11-148E17.1; CTD-2384A14.1*
207	14	30003271	30452969	*CTD-2503I6.1; AL356756.1; RNU6-1234P; RP11-269C4.2; CTD-2251F13.1; PRKD1*
209	14	33643137	33657980	*NPAS3*
211	14	55335061	55485150	*MIR4308; FDPSP3; AL160471.6; GCH1; WDHD1*
212	14	60099667	60168672	*MIR5586; RTN1*
213	14	73281471	73983422	*Y_RNA; snoU13; RP1-146I3.1; RP11-109N23.6; RP11-109N23.1; RN7SL586P; RP11-109N23.4; RP11-109N23.5; RP4-687K1.2; RNU6-419P; RP4-647C14.3; AC005280.1; C14orf169; ZFYVE1; RP4-647C14.2; PAPLN; RP1-240K6.3; HEATR4; DPF3; RBM25; PSEN1; NUMB; DCAF4*
214	14	104009938	104363528	*RNU7-160P; RNU4-68P; BAG5; AL139300.1; RP11-894P9.1; RP11-73M18.6; RP11-73M18.10; RP11-73M18.7; RP11-73M18.8; RP11-73M18.9; AL049840.1; Y_RNA; RP11-73M18.11; SNORD51; CTD-2134A5.3; RP11-894P9.2; XRCC3; ZFYVE21; LINC00637; CTD-2134A5.4; KLC1; RP11-73M18.2; APOPT1; PPP1R13B*
217	15	61831679	61910113	*RP11-259A24.1; RP11-507B12.2*
219	15	78535049	78602774	*RP11-762H8.4; RP11-762H8.2; RP11-762H8.1; RP11-762H8.3; DNAJA4; WDR61; ACSBG1*
220	15	82426169	83403726	*RNU1-77P; AC135995.1; RN7SL61P; DNM1P38; RP13-608F4.6; RPS17;RN7SL256P; AC126339.1; RP13-608F4.5; AC010724.1;RN7SL410P; GOLGA6L21P; DNM1P42; RPS17L;RP11-752G15.4; AC105339.1; RP11-752G15.9; AC105339.2; ADAMTS7P1; GOLGA6L10; RP13-608F4.8CSPG4P8; RP11-152F13.3; GOLGA6L17PGOLGA6L9ADAMTS7P2; GOLGA6L18;*

Locus	Chr	Start	Stop	Genes
				CSPG4P9; UBE2Q2P3GOLGA6L19; CSPG4P10; RP13-996F3.3; RP11-152F13.10; RP11-752G15.3UBE2Q2P2; UBE2Q2P6EFTUD1; FAM154B;RP11-152F13.7;RPL9P8RP11-152F13.8; GOLGA6L20; RP11-379H8.1; CPEB1; AP3B2
223	16	9875512	9970227	*GRIN2A*
224	16	13638746	13638747	*U91319.1*
227	16	67379246	68419298	*RNU1-123P; TPPP3; RP11-297D21.2; AC009061.1; AGRP; CTD-2012K14.2; CTD-2012K14.3; CTD-2012K14.4; CTD-2012K14.7; AC009095.4; ACD; PARD6A; C16orf86; RP11-167P11.2; THAP11; CTC-479C5.11; AC040162.1; NRN1L; CTC-479C5.10; CTRL; CTC-479C5.12; PSMB10; CTC-479C5.17; KARSP3; DDX28; CTC-479C5.6; RNU6-359P; AC130462.1; Y_RNA; SNORA48; RP11-96D1.9; RPS12P27; RP11-96D1.5; ESRP2; RP11-96D1.10; RP11-96D1.11; RP11-96D1.6; RP11-96D1.7; RNU6-1262P; snoU13; RP11-96D1.3; RNU4-30P; ZDHHC1; HSD11B2; RP11-297D21.4; CTD-2012K14.6; FAM65A; ENKD1; GFOD2; RLTPR; TSNAXIP1; CENPT; EDC4; PSKH1; LCAT; SLC12A4; DPEP3; RP11-67A1.2; SLC7A6SLC7A6OS; PRMT7; RANBP10; NUTF2; DPEP2; DUS2; LRRC36; ATP6V0D1; CTCF; PLA2G15; SMPD3; NFATC3*
228	16	71472130	71925885	*RP11-510M2.8; RP11-510M2.5; RNU6-1061P; RP11-432I5.1; TAT; RP11-432I5.2; RNU6-208P; SNORA70D; RP11-432I5.8; RP11-432I5.4; SNORD71; RP11-417N10.3; RP11-498D10.3; RP11-510M2.2; RP11-510M2.6; ZNF23; AC010547.9; MARVELD3; ATXN1L; ZNF821; RP11-432I5.6; ZNF19; CHST4; PHLPP2; AP1G1; IST1*
229	16	72993621	73021220	*AC132068.1; ZFHX3*
230	16	82643729	82666923	*CDH13*
231	16	83171314	83205290	*CDH13*
232	16	89645436	89754694	*DPEP1; CHMP1A; SPATA33; CDK10; RP11-368I7.4; CPNE7*
233	17	17535595	18036283	*RAI1-AS1; SMCR5; RP1-253P7.1; MIR33B; AC122129.1; AC087163.3; Y_RNA; AC087163.2; SMCR2; SREBF1; LRRC48; ATPAF2; DRG2; MYO15A; RAI1; GID4; TOM1L2*
234	17	27662128	28553639	*RPL35AP35; RNU4-34P; MIR4523; RNU6-711P; RNU6-1034P; ABHD15; TP53I13; RP11-68I3.4;RP11-68I3.7; RP11-68I3.10; CORO6; RNU6-920P; RP11-68I3.11; RPL21P123; RP11-82O19.2; SNORA70; RPL9P30; RP11-338L22.2; snoU13; RP11-338L22.3; AC104996.1; RNY4P13; RNY4P13; AC104984.4; RP11-1148O4.1; MIR3184; MIR423; RP11-354P11.3; RP11-354P11.8; RP11-354P11.4; RP11-296K13.4; MIR4523; RP11-68I3.5; RP11-82O19.1; SLC6A4; TAOK1; GIT1; ANKRD13B; SSH2; RP11-68I3.2; RP11-1148O4.2; NSRP1; EFCAB5*
235	17	34825860	34961051	*RNA5SP439; PIGW; DHRS11; ZNHIT3; CTB-75G16.1; GGNBP2; MRM1; MYO19*
237	17	46835628	47047868	*RN7SL125P; SNORA68; RP11-463M16.5; RP11-501C14.9; AC091133.1; RNU1-42P; snoU13; TTLL6; ATP5G1; UBE2Z; SNF8; GIP; SUMO2P17; CALCOCO2*
238	17	65463333	65482109	*MIR548AA2; PITPNC1*
242	18	50555224	51061399	*hsa-mir-4528; RP11-671P2.1; DCC*
244	18	53186091	53186092	*TCF4*

Locus	Chr	Start	Stop	Genes
245	18	68196166	68388032	*GTSCR1*
246	18	77551585	77580712	*RP11-154H12.3*
247	19	2253589	2281997	*OAZ1; JSRP1; C19orf35*
249	19	13037733	13194772	*CTC-425F1.4; CALR; AC092069.1; GADD45GIP1 DAND5 CTC-239J10.1 AC007787.2 CTC-425F1.2 FARSA RAD23A NFIX*
250	19	18466839	18466840	*PGPEP1*
252	19	50941806	51029602	*CTD-2545M3.2; EMC10; CTD-2545M3.8; JOSD2; ASPDH; MYBPC2; FAM71E1; LRRC4B*
253	20	16025288	16025289	*MACROD2*
254	20	16339568	16452607	*AL118509.1; KIF16B*
257	20	58989893	59049432	*MTCO2P1; RP5-1043L13.1*
258	21	24763159	24804929	*EEF1A1P1; TUBAP; Y_RNA*
260	22	20811230	20946457	*KLHL22-IT1; Y_RNA; RN7SL812P; KRT18P5; AC007731.1; AC007050.17; AC007050.18; MED15;KLHL22*
261	22	28268650	29340914	*MIR3199-2; RN7SL757P; SNORD42; Y_RNA; RN7SL162P; CTA-292E10.8; CTA-292E10.7; TTC28-AS1; HSCBCCDC117; XBP1; TTC28; CTA-292E10.6; CHEK2; PITPNB; ZNRF3*
262	22	31497053	31532568	*RP3-412A9.12; PLA2G3; SMTN; SELM; INPP5J*
263	22	34265386	34266265	*LARGE*
266	22	48133457	48183889	*RP11-191L9.4*

Supplementary Table 5. 8: Genes that Map to Unique Loci Jointly Associated with Cognitive Factor 3 and Schizophrenia

Locus	Chr	Start	Stop	Genes
1	1	6776009	6786581	*RP11-242F24.1*
2	1	8404092	8888842	*SNORA77; RP5-1115A15.2; RPL7P11; RPL7P7; Y_RNA; RP4-633I8.3; RP4-633I8.4; RP5-1115A15.1; RERE; SLC45A1*
4	1	35898837	36317471	*RP4-728D4.3; RP4-728D4.2; RN7SL281P; C1orf216; NCDN; PSMB2; RP11-435D7.3; CLSPN; KIAA0319L; TFAP2E; AGO4*
6	1	49450307	50591851	*snoU13; RP5-926E3.1; ZNF859P; AL645730.1; AL645730.2; MTND2P29; RP11-492I2.1; RP11-141A19.2; AGBL4-IT1; RP11-141A19.1; ELAVL4; AGBL4*
7	1	65615967	65679229	*RP4-700A9.1; AK4*
8	1	66304166	66333877	*PDE4B*
11	1	115382353	115424600	*NR1H5P; SYCP1*
12	1	163582979	163810259	*RP4-640E24.1; RP4-640E24.1*
13	1	183289522	183372586	*NMNAT2*
14	1	190757035	191065967	*RP11-463J7.3; RP11-463J7.2*
15	1	243282561	243612050	*RP11-261C10.4; AC092782.1; FCF1P7; MIR4677; RP11-261C10.5; CEP170; SDCCAG8*
16	2	7589080	7805263	*RNU6ATAC37P; AC013460.1*
20	2	56439551	56501235	*RNA5SP93; RP11-482H16.1; CCDC85A*
24	2	76239790	76545193	*SUCLA2P2; AC073091.2; RP11-335E8.1*
28	2	172521826	172922663	*AC068039.1; AC068039.4; RNU6-182P; DYNC1I2; HAT1; SLC25A12; METAP1D*
29	2	174927432	175153974	*RP11-451F14.1; RN7SL65P; Y_RNA; OLA1*
31	2	189105221	189415219	*RNA5SP114; MIR561; GULP1; LINC01090*
34	2	233557989	233815353	*AC064852.5; AC064852.5; AC064852.4; RNU6-107P; Y_RNA; KCNJ13; C2orf82; GIGYF2; NGEF*
35	3	2568329	2576606	*CNTN4*
39	3	29475290	29480453	*RBMS3*
41	3	38075010	38320202	*PPP2R2DP1; Y_RNA; MYD88; RP11-815I22.1; SLC22A13; ACAA1; DLEC1; OXSR1*
44	3	71127044	71274820	*FOXP1*
45	3	76195847	76270678	*ROBO2*
47	3	107754561	107845839	*RP11-861A13.4; CD47*

Locus	Chr	Start	Stop	Genes
48	3	135814008	136615268	*TDGF1P6; RP11-463H24.1; RNU6-1284P; RNY4P4; HMGN1P10; RNU7-198P; RNU6-789P; RP11-102M11.1; RP11-102M11.2; RP11-731C17.2; MSL2; RP11-731C17.1; SLC35G2; NCK1; PPP2R3A; PCCB; RP11-85F14.5; STAG1*
49	3	177314667	177333565	*LINC00578*
53	4	90628126	90808918	*RP11-67M1.1; RP11-115D19.1; SNCA; MMRN1*
55	4	153034858	153075714	*RP11-18H21.2*
56	5	59087285	59133111	*PDE4D*
57	5	67668469	67734270	*CTD-2582M21.1; CTC-537E7.3*
58	5	106876424	107049989	*RP11-252I13.2; EFNA5*
59	5	168677339	168697807	*MIR585; SLIT3*
65	6	68940882	69047072	*RP11-406O16.1*
66	6	70077269	70077270	*BAI3*
67	6	84223562	84409255	*PRSS35; SNAP91*
68	6	96421921	96477293	*KRT18P50; FUT9*
70	6	113003527	113205566	*RP11-505K1.1*
71	6	119310118	119353212	*RP11-351A11.1; FAM184A*
73	6	130544508	130772152	*AL137251.1; TMEM200A; SAMD3*
74	6	131136312	131385009	*SMLR1; EPB41L2*
75	6	140365270	141320845	*RNA5SP220; MIR3668; AL356137.1; MIR4465; RPS3AP24; RP3-460G2.2; RP11-471B18.1; RP3-332B22.1*
77	7	23713061	23927052	*AC006026.13; AC006026.13; PCMTD1P3; TPT1P7; FAM221A; STK31*
80	7	82097923	82555669	*MTHFD2P5; AC004006.2; PCLO*
82	7	103672959	103870219	*ORC5*
84	7	110111383	110265344	*AC003088.1*
85	7	110821729	111236477	*AC003989.3; AC003989.4; IMMP2L*
86	7	121993482	122020759	*RP5-1101C3.1; CADPS2*
88	7	147024220	147184599	*MIR548F4; CNTNAP2*
92	8	131084727	131361477	*AC131568.1; SNORA12; ASAP1*

Locus	Chr	Start	Stop	Genes
93	8	135795756	135844738	*MIR30B; MIR30D; AC083843.1*
97	9	32932193	33101838	*ASS1P12; TCEA1P4; RP11-54K16.2; AL162590.1; APTX; SMU1; DNAJA1*
98	9	77265631	77298426	*RORB*
101	9	122042537	122116973	*BRINP1*
104	10	15306519	15483645	*FAM171A1*
105	10	52901140	52909235	*PRKG1*
106	10	64131277	64194815	*ZNF365*
107	10	93677995	94198194	*SNORA25; SDHCP2; AL158040.1; CPEB3_ribozyme; NHP2P1; Y_RNA; MARK2P9; EIF4A1P8; BTAF1; CPEB3; 44990*
109	11	1507511	1633238	*KRTAP5-2; KRTAP5-3; MOB2; DUSP8; KRTAP5-1; KRTAP5-AS1*
110	11	17933320	18065861	*RP1-59M18.2; TPH1; SERGEF*
111	11	27924493	28577867	*MIR610; RP11-797J4.1; RN7SKP158; AC104978.1; RP11-22P4.2; RP11-406D1.2; KIF18A; RP11-22P4.1; METTL15*
112	11	29828545	29941321	*CTD-3138F19.1*
115	11	63587116	63776265	*RP11-466C23.5; RNU6-1306P; RCOR2; COX8A; RNU6-45P; C11orf84; MARK2; NAA40; AP000721.4; OTUB1; MACROD1*
117	11	134261149	134294813	*B3GAT1*
119	12	23027721	23078449	*RP11-114G22.1*
120	12	24412869	24441358	*RP11-444D3.1*
121	12	45850021	45932457	*RP11-352M15.1*
125	12	121188640	121351934	*ARF1P2; RP11-173P15.7; SPPL3*
127	12	124388510	124500725	*RP11-380L11.4; DNAH10OS; RP11-380L11.3; RP11-214K3.23; RP11-214K3.22; RP11-214K3.21; RP11-214K3.19; RP11-214K3.18; RP11-214K3.5; RP11-214K3.20; CCDC92; ZNF664; DNAH10; FAM101A*
128	13	30079874	30155874	*SLC7A1*
129	13	58250321	59207912	*RNA5SP30; RNY4P29; CTAGE16P; PCDH17; LINC00374*
132	13	96340600	96815076	*MTND5P2; MTND6P18; MTCYBP3; snR65; HMGN1P24; DNAJC3; HS6ST3; UGGT2*
133	13	109719313	109777503	*MYO16-AS2; MYO16*
134	13	111978919	112037454	*TEX29*

Locus	Chr	Start	Stop	Genes
136	14	52896567	53067681	*TXNDC16; GPR137C*
137	14	71355047	71612951	*RP5-1163L11.2; RP5-1163L11.3; PTTG4P; RP6-91H8.3; PCNX*
138	15	26677808	26683941	*AC009878.2*
141	15	48019015	48095645	*CTD-2270N23.1; RP11-198M11.2; SEMA6D*
142	15	59305087	59444018	*RP11-59H7.1; C15ORF31; AC092757.1; RP11-59H7.3; CCNB2; RNF111; MYO1E*
143	15	78802295	78864024	*AC027228.1; HYKK; PSMA4; CHRNA5*
144	15	83523162	83977166	*AC022558.1; RP11-90B9.2; RP11-382A20.1; MIR4515; RP11-382A20.2; RP11-382A20.7; FAM103A1; C15orf40; BTBD1; TM6SF1; HDGFRP3; BNC1; RP11-382A20.5; RP11-382A20.6; HOMER2; RP11-382A20.4*
145	15	92698642	92722801	*RP11-24J19.1; RP11-24J19.1; RP11-152L20.3; SLCO3A1*
147	16	4450420	4596447	*DNAJA3; NMRAL1; HMOX2; CORO7-PAM16; CORO7; CDIP1*
149	16	7742887	7760846	*RBFOX1*
151	16	83428620	83442229	*AC009142.1; RP11-543N12.1; CDH13*
152	16	85106499	85133610	*FAM92B; KIAA0513*
153	16	85681434	85728651	*RN7SL381P; GSE1; C16orf74; GINS2*
154	17	1235765	1374195	*RP11-818O24.3; YWHAE; CRK; MYO1C*
155	17	7093465	7185092	*MIR324; DVL2; PHF23; CTD-2545G14.7; CTDNEP1; CLDN7; Y_RNA; SLC2A4; DLG4; ACADVL; GABARAP; RP1-4G17.5; ELP5*
156	17	27463463	27632374	*RP11-22N12.2; TWF1P1; MYO18A; RP11-321A17.4; CRYBA1; NUFIP2*
158	17	56423749	57205464	*AC023992.1; RP11-112H10.6; C17orf47; U3; RNU1-60P; CTD-2200P10.1; RNU1-108P; CTD-2200P10.3; RNU1-52P; RNU1-85P; RNU6-518P; RP11-579O24.1; RP11-579O24.3; AC100832.1; RN7SL716P; AC099850.1; SUPT4H1; HSF5; MTMR4; RAD51C; SKA2; BZRAP1-AS1; RNF43; TEX14; PPM1E; TRIM37; RP11-112H10.4*
159	17	75857636	75898770	*FLJ45079*
161	18	6879352	6922747	*LINC00668; ARHGAP28*
163	18	39144763	39291937	*RP11-142I20.1*
165	18	53195248	53455329	*RPL21P126; RP11-397A16.1; RP11-397A16.2; TCF4*
166	18	77405226	77543315	*RP11-567M16.3; RP11-567M16.5; CTDP1*
167	19	49639947	49656358	*HRC; PPFIA3*

Locus	Chr	Start	Stop	Genes
168	19	51164802	51164803	*SYT3*
172	22	34116863	34124976	*LARGE-IT1; LARGE-AS1; LARGE*

Supplementary Table 5. 9: Gene-set Analysis Results for Unique Loci Jointly Associated with Cognitive Factor 1 and Schizophrenia

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GO_bp	GO_CYTOSOLIC_TRANSPORT	151	7	2.19E-06	1.61E-02	*MAPK3:CORO1A:TBC1D10B:GOSR1:PLEKHJ1:DOPEY2:TBC1D5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_CYTOSOLIC_TRANSPORT
GO_bp	GO_REGULATION_OF_VESICLE_MEDIATED_TRANSPORT	510	11	4.84E-06	1.78E-02	*CACNB2:RAB8B:DOC2A:MAPK3:CORO1A:GOSR1:KCNB1:TBC1D5:RUFY1:MAGI2:DGKI*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_REGULATION_OF_VESICLE_MEDIATED_TRANSPORT
GWAScatalog	Schizophrenia	727	36	3.64E-31	6.61E-28	*CACNB2:ANK3:SHMT2:NDUFA4L2:STAC3:R3HDM2:BCL11B:ASPHD1:KCTD13:TMEM219:TAOK2:HIRIP3:INO80E:DOC2A:FAM57B:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CEBPZ:NDUFAF7:PRKD3:QPCT:KCNB1:PTGIS:TBC1D5:KALRN:NEK1:CLCN3:GPM6A:GRIA1:MAGI2:DGKI:GABBR2*	NA
GWAScatalog	Autism spectrum disorder or schizophrenia	612	22	1.10E-15	9.98E-13	*CACNB2:SHMT2:NDUFA4L2:STAC3:R3HDM2:ASPHD1:KCTD13:TMEM219:TAOK2:HIRIP3:INO80E:DOC2A:FAM57B:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:NEK1:CLCN3:DGKI*	NA
GWAScatalog	Body fat distribution (arm fat ratio)	129	13	3.11E-15	1.88E-12	*ASPHD1:KCTD13:TMEM219:TAOK2:HIRIP3:INO80E:DOC2A:FAM57B:ALDOA:PPP4C:TBX6:YPEL3:GDPD3*	NA
GWAScatalog	Chronic obstructive pulmonary disease or high blood pressure (pleiotropy)	72	8	3.91E-10	1.77E-07	*TMEM219:TAOK2:HIRIP3:INO80E:DOC2A:FAM57B:ALDOA:PPP4C*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GWAScatalog	Cognitive ability, years of educational attainment or schizophrenia (pleiotropy)	165	6	4.79E-05	1.74E-02	*CACNB2:SHMT2:TAOK2:PDIA6:GPM6A:TTLL11*	NA
GO_cc	GO_SYNAPSE_PART	928	14	1.38E-05	1.38E-02	*CACNB2:ANK3:HTR3B:RAB8B:DOC2A:AP3D1:KCNB1:CLCN3:GPM6A:GRIA1:SYNE1:MAGI2:DGKI:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_SYNAPSE_PART
GO_cc	GO_MEMBRANE_PROTEIN_COMPLEX	1140	15	3.25E-05	1.39E-02	*CACNB2:HTR3B:NDUFA4L2:STAC3:TRPC4:APH1B:GOSR1:AP3D1:ATP6V1C2:KCNB1:TBC1D5:SCLT1:GRIA1:SYNE1:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_MEMBRANE_PROTEIN_COMPLEX
GO_cc	GO_SYNAPSE	1165	15	4.17E-05	1.39E-02	*CACNB2:ANK3:HTR3B:RAB8B:DOC2A:CORO1A:AP3D1:KCNB1:CLCN3:GPM6A:GRIA1:SYNE1:MAGI2:DGKI:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_SYNAPSE
GO_cc	GO_POSTSYNAPSE	607	10	1.31E-04	3.05E-02	*ANK3:HTR3B:AP3D1:KCNB1:GPM6A:GRIA1:SYNE1:MAGI2:DGKI:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_POSTSYNAPSE
GO_cc	GO_ENDOSOME	879	12	1.58E-04	3.05E-02	*RAB8B:APH1B:MAPK3:CORO1A:AP3D1:PLEKHJ1:DOPEY2:TBC1D5:CLCN3:GRIA1:RUFY1:MAGI2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_ENDOSOME
GO_cc	GO_CATION_CHANNEL_COMPLEX	219	6	2.26E-04	3.05E-02	*CACNB2:HTR3B:STAC3:TRPC4:KCNB1:GRIA1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_CATION_CHANNEL_COMPLEX
GO_cc	GO_POSTSYNAPTIC_MEMBRANE	320	7	2.67E-04	3.05E-02	*ANK3:HTR3B:KCNB1:GRIA1:SYNE1:DGKI:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_POSTSYNAPTIC_MEMBRANE
GO_cc	GO_NEURON_PART	1700	17	2.72E-04	3.05E-02	*CACNB2:ANK3:HTR3B:PCDH9:BCL11B:RAB8B:TAOK2:DOC2A:CORO1A:AP3D1:KCNB1:*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_NEURON_PART

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						CLCN3:GPM6A:GRIA1:MAGI2:DGKI:GABBR2	
GO_cc	GO_SYNAPTIC_MEMBRANE	427	8	2.75E-04	3.05E-02	*ANK3:HTR3B:KCNB1:GPM6A:GRIA1:SYNE1:DGKI:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_SYNAPTIC_MEMBRANE
GO_cc	GO_NEURON_PROJECTION	1295	14	4.80E-04	4.80E-02	*ANK3:HTR3B:PCDH9:BCL11B:TAOK2:DOC2A:CORO1A:AP3D1:KCNB1:GPM6A:GRIA1:MAGI2:DGKI:GABBR2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_NEURON_PROJECTION
Positional_gene_sets	chr16p11	112	21	3.46E-30	1.03E-27	*ASPHD1:KCTD13:TMEM219:TAOK2:HIRIP3:INO80E:DOC2A:FAM57B:ALDOA:PPP4C:TBX6:YPEL3:GDPD3:MAPK3:CORO1A:BOLA2B:SLX1A:SULT1A3:RP11-347C12.1:CD2BP2:TBC1D10B*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr16p11
Positional_gene_sets	chr2p22	41	4	2.02E-05	3.02E-03	*CEBPZ:NDUFAF7:PRKD3:QPCT*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr2p22
Positional_gene_sets	chr4q33	6	2	2.28E-04	2.27E-02	*NEK1:CLCN3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr4q33
microRNA_targets	TGCAAAC_MIR452	106	5	6.20E-05	1.37E-02	*CACNB2:ANK3:PCDH9:RAB8B:DOC2A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGCAAAC_MIR452

Supplementary Table 5. 10: Gene-set Analysis Results for Unique Loci Jointly Associated with Cognitive Factor 2 and Schizophrenia

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GO_bp	GO_HOMOPHILIC_CELL_ADHESION_VIA_PLASMA_MEMBRANE_ADHESION_MOLECULES	163	19	3.81E-08	2.80E-04	*CDH13:CELSR3:CDHR4:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:SDK1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_HOMOPHILIC_CELL_ADHESION_VIA_PLASMA_MEMBRANE_ADHESION_MOLECULES
GO_bp	GO_CELL_CELL_ADHESION_VIA_PLASMA_MEMBRANE_ADHESION_MOLECULES	267	23	4.07E-07	1.49E-03	*CDH13:LRRC4B:CELSR3:AMIGO3:CDHR4:ALCAM:EFNA5:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:SDK1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_CELL_CELL_ADHESION_VIA_PLASMA_MEMBRANE_ADHESION_MOLECULES
GWAS catalog	Schizophrenia	727	112	4.51E-56	8.19E-53	*BRINP2:PRKG1:TMTC1:TAC3:MYO1A:TMEM194A:NAB2:STAT6:PPFIA2:PRKD1:NPAS3:RTN1:BAG5:KLC1:APOPT1:XRCC3:ZFYVE21:PPP1R13B:CPEB1:AP3B2:GRIN2A:RLTPR:ACD:PARD6A:ENKD1:GFOD2:RANBP10:TSNAXIP1:CENPT:THAP11:NUTF2:EDC4:NRN1L:PSKH1:CTRL:PSMB10:LCAT:SLC12A4:DPEP3:DPEP2:DUS2:DDX28:NFATC3:ESRP2:PLA2G15:SLC7A6:SLC7A6OS:CDH13:RAI1:SREBF1:TOM1L2:LRRC48:ATPAF2:GID4:DRG2:MYO15A:DCC:TCF4:PPP3R1:ANKRD44:SF3B1:COQ10B:HSPD1:HSPE1:HSPE1-MOB4:MOB4:RFTN2:MARS2:BOLL:PLCL1:SPAG16:TBC1D5:TRANK1:GNAT1:HYAL3:RASSF1:FOXP1:BANK1:SLC39A8:CISD2:SLC9B1:BDH2:CENPE:GPM6A:SRA1:CD14:NDUFA2:TMCO6:IK:WDR55:DND1:HARS:HARS2:ZMAT2:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA13:PCDHAC2:SY*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						NGAP1:NKAIN2:CALN1:DGKI:CSMD1:SPATA31D1	
GWAS catalog	Sleep duration (short sleep)	94	40	6.38E-39	5.79E-36	*TCF4:USP4:GPX1:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:FAM212A:UBA7:TRAIP:CAMKV:MST1R:MON1A:RBM6:RBM5:SEMA3F:GNAT1:GNAI2:LSMEM2:IFRD2:HYAL3:NAT6:HYAL1:HYAL2:TUSC2:RASSF1:ZMYND10:NPRL2:CYB561D2:TMEM115:CACNA2D2:SLC39A8*	NA
GWAS catalog	Extremely high intelligence	81	32	4.42E-30	2.67E-27	*CDC42:WNT4:FOXO6:ARHGAP15:TANK:GPX1:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:CDHR4:FAM212A:UBA7:TRAIP:CAMKV:MST1R:MON1A:RBM6:RBM5:SEMA3F:GNAT1:TET2:PPA2:APBA1*	NA
GWAS catalog	Intelligence (MTAG)	246	40	5.94E-21	2.42E-18	*FOXO6:SORCS3:PRKD1:EFTUD1:ZNF19:IST1:GGNBP2:DCC:NFIX:BCL11A:PPP3R1:MACROD2:LARGE:NCKIPSD:USP4:GPX1:NICN1:DAG1:BSN:IP6K1:TRAIP:CAMKV:MON1A:RBM6:SEMA3F:CACNA2D2:FOXP1:BANK1:SLC39A8:TET2:PPA2:MAML3:FBXL17:PHF1:ZMIZ2:CALN1:CALU:PTPRN2:ELAVL2:APBA1*	NA
GWAS catalog	Crohn's disease	625	63	6.66E-21	2.42E-18	*STIP1:FERMT3:TRPT1:NUDT22:DNAJC4:VEGFB:FKBP2:PSMB10:CDH13:EFR3B:POMC:HSPE1-MOB4:MOB4:RFTN2:MARS2:BOLL:PLCL1:PLXNB1:CCDC51:TMA7:ATRIP:TREX1:SHISA5:PFKFB4:UCN2:COL7A1:UQCRC1:TMEM89:SLC26A6:CELSR3:NCKIPSD:IP6K2:PRKAR2A:SLC25A20:ARIH2OS:ARIH2:P4HTM:WDR6:DALRD3:NDUFAF3:IMPDH2:QRICH1:QARS:USP19:LAMB2:CCDC71:KLHDC8B:CCDC36:USP4:GPX1:RHOA:TCTA:AMT:NICN1:*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						DAG1:BSN:APEH:MST1:RNF123:FOXP1:BANK1:SLC39A8:CDKAL1	
GWAS catalog	General cognitive ability	190	35	2.71E-20	8.21E-18	*FOXO6:GATAD2B:ANKRD45:PRKD1:EFTUD1:FAM154B:CPEB1:AP1G1:RAI1:DCC:BCL11A:PPP3R1:TANK:MACROD2:LARGE:IP6K2:RHOA:NICN1:BSN:IP6K1:CDHR4:CAMKV:RBM6:SEMA3F:GNAT1:FOXP1:BANK1:SLC39A8:TET2:PPA2:CDKAL1:ZMIZ2:AUTS2:CALN1:ELAVL2*	NA
GWAS catalog	Regular attendance at a religious group	70	23	8.12E-20	2.11E-17	*TCF4:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:CDHR4:FAM212A:UBA7:TRAIP:CAMKV:MST1R:MON1A:RBM6:TET2:PPA2*	NA
GWAS catalog	Regular attendance at a gym or sports club	38	18	3.26E-19	7.39E-17	*TCF4:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:CDHR4:FAM212A:UBA7:TRAIP:CAMKV:MST1R:MON1A:RBM6:RBM5:SEMA3F*	NA
GWAS catalog	Ulcerative colitis	460	50	4.13E-18	8.33E-16	*RFTN2:PLCL1:PLXNB1:CCDC51:TMA7:ATRIP:TREX1:SHISA5:PFKFB4:UCN2:COL7A1:UQCRC1:TMEM89:SLC26A6:CELSR3:NCKIPSD:IP6K2:PRKAR2A:SLC25A20:ARIH2OS:ARIH2:P4HTM:WDR6:DALRD3:NDUFAF3:IMPDH2:QRICH1:QARS:USP19:LAMB2:CCDC71:KLHDC8B:CCDC36:USP4:GPX1:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:UBA7:MST1R:MANBA*	NA
GWAS catalog	Empathy quotient	14	12	5.82E-18	1.06E-15	*GATAD2B:DENND4B:CRTC2:SLC39A1:CREB3L4:ZDHHC1:HSD11B2:ATP6V0D1:ENKD1:GFOD2:RANBP10:TSNAXIP1*	NA
GWAS catalog	Morning person	200	31	6.78E-16	1.12E-13	*TAT:MARVELD3:ZFHX3:PITPNC1:TCF4:BCL11A:ARHGAP15:ANKRD44:SF3B1:COQ10B:RFTN2:MARS2:BOLL:PLCL1:TRANK1:PFKFB4:IP6K2:PRKAR2*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						A:ARIH2:QARS:RHOA:BSN:RNF123:CAMKV:RBM6:RBM5:SEMA3F:GNAI2:CACNA2D2:DOCK3:CSMD1	
GWAS catalog	Age at first birth	28	14	1.20E-15	1.81E-13	*GATAD2B:DENND4B:CRTC2:SLC39A1:CREB3L4:LARGE:RNF123:CAMKV:MST1R:MON1A:RBM6:RBM5:SEMA3F:HYAL3*	NA
GWAS catalog	Body mass index	1199	80	1.80E-15	2.51E-13	*SNX27:PRKG1:PLEKHA7:RPS13:PIK3C2A:NUCB2:NCR3LG1:KCNJ11:ABCC8:MACROD1:MAP3K12:PRKD1:NPAS3:BAG5:KLC1:APOPT1:XRCC3:ZFYVE21:PPP1R13B:SLC7A6:PRMT7:ZFHX3:CPNE7:RAI1:ZNHIT3:MYO19:PIGW:GGNBP2:DHRS11:MRM1:DCC:NFIX:PGPEP1:EFR3B:POMC:CTNNA2:LRP1B:SPAG16:MACROD2:KIF16B:TTC28:DAG1:BSN:APEH:MST1:RNF123:IP6K1:CDHR4:FAM212A:UBA7:MST1R:MON1A:RBM6:RBM5:SEMA3F:GNAT1:GNAI2:LSMEM2:IFRD2:HYAL3:HYAL2:NPRL2:ALCAM:IGF2BP2:SLC39A8:EFNA5:FBXL17:CDKAL1:VPS52:RPS18:B3GALT4:WDR46:KIFC1:PHF1:CUTA:SYNGAP1:KLHL32:AUTS2:DGKI:ELAVL2*	NA
GWAS catalog	Cognitive ability, years of educational attainment or schizophrenia (pleiotropy)	165	27	1.33E-14	1.72E-12	*FOXO6:SORCS3:RARG:PRKD1:KLC1:APOPT1:CPEB1:GRIN2A:SMPD3:CDH13:DCC:TCF4:BCL11A:LRP1B:SF3B1:RBM6:FOXP1:SLC39A8:TET2:MAML3:GPM6A:EFNA5:FBXL17:CALN1:PTPRN2:APBA1:BRD3*	NA
GWAS catalog	Mood instability	61	17	1.20E-13	1.45E-11	*SORCS3:DCC:TCF4:LRP1B:ARHGAP15:PLCL1:PLCL2:NDUFAF3:QARS:LAMB2:CCDC36:GPX1:RHOA:NICN1:DAG1:BSN:AMIGO3*	NA
GWAS catalog	Inflammatory bowel disease	727	52	2.03E-11	2.30E-09	*FLRT1:TRPT1:EFR3B:POMC:PLXNB1:CCDC51:TMA7:ATRIP:TREX1:SHISA5:PFKFB4:UCN2:COL7A1:UQCRC1:TMEM89:SLC26A6:CELSR3:NCKIPSD:IP*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						6K2:PRKAR2A:SLC25A20:ARIH2OS:ARIH2:P4HTM:WDR6:DALRD3:NDUFAF3:IMPDH2:QRICH1:QARS:USP19:LAMB2:CCDC71:KLHDC8B:CCDC36:USP4:GPX1:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:IP6K1:MST1R:FOXP1:BANK1:SLC39A8:CDKAL1	
GWAS catalog	Multisite chronic pain	33	10	5.85E-09	6.25E-07	*SORCS3:NUMB:DCC:CTNNA2:RNF123:AMIGO3:GMPPB:SLC39A8:MAML3:SDK1*	NA
GWAS catalog	Autism spectrum disorder or schizophrenia	612	41	1.98E-08	2.00E-06	*BRINP2:PRKG1:BAG5:KLC1:APOPT1:XRCC3:ZFYVE21:PPP1R13B:GRIN2A:TCF4:ANKRD44:SF3B1:COQ10B:HSPD1:HSPE1:HSPE1-MOB4:MOB4:RFTN2:MARS2:BOLL:PLCL1:TRANK1:FOXP1:BANK1:SLC39A8:VPS52:RPS18:B3GALT4:WDR46:PFDN6:RGL2:TAPBP:ZBTB22:DAXX:KIFC1:PHF1:CUTA:SYNGAP1:ZBTB9:DGKI:SPATA31D1*	NA
GWAS catalog	Chronotype	549	35	7.19E-07	6.87E-05	*GATAD2B:RABGAP1L:GCH1:WDHD1:NFATC3:TAT:MARVELD3:ZFHX3:CALCOCO2:PITPNC1:TCF4:PGPEP1:BCL11A:ARHGAP15:TANK:MLTK:PLCL1:MACROD2:KIF16B:TTC28:TRANK1:RBM6:CACNA2D2:FOXP1:ALCAM:PPP3CA:CCRN4L:EFNA5:SYNGAP1:AUTS2:CALN1:FEZF1:CSMD1:SPATA31D1:IER5L*	NA
GWAS catalog	Sum basophil neutrophil counts	117	14	1.72E-06	1.56E-04	*PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:BRD3*	NA
GWAS catalog	Cognitive ability (MTAG)	49	9	3.54E-06	3.06E-04	*SORCS3:EFTUD1:DCC:BCL11A:PLCL2:CELSR3:FOXP1:TET2:APBA1*	NA
GWAS catalog	Blood protein levels	1656	72	5.31E-06	4.38E-04	*CREB3L4:PRDX6:PLEKHA7:NUCB2:MLF2:LRRC36:TPPP3:ZDHHC1:HSD11B2:ATP6V0D1:AGRP:FAM65A:SMPD3:ZNF19:IST1:DPEP1:CALCOCO2:SE*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						MA4C:LARGE:PLCL2:COL7A1:TMEM89:SLC26A6:CELSR3:NCKIPSD:IP6K2:PRKAR2A:SLC25A20:ARIH2OS:ARIH2:P4HTM:WDR6:DALRD3:NDUFAF3:IMPDH2:QRICH1:QARS:USP19:LAMB2:CCDC71:KLHDC8B:CCDC36:USP4:GPX1:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:TRAIP:CAMKV:RBM6:RBM5:NPRL2:MAPKAPK3:DOCK3:ALCAM:BANK1:MANBA:CD14:NDUFA2:TAPBP:ADAM22:ZFPM2:CRAT	
GWAS catalog	General risk tolerance (MTAG)	247	20	5.93E-06	4.57E-04	*SORCS3:WSCD2:PRKD1:PPP1R13B:GRIN2A:ZNF23:ZFHX3:CDH13:TCF4:BCL11A:LRP1B:MACROD2:TBC1D5:SATB1:SEMA3F:FOXP1:TET2:ATG10:AUTS2:DGKI*	NA
GWAS catalog	TB-LM or TBLH-BMD (pleiotropy)	6	4	6.04E-06	4.57E-04	*WNT4:SREBF1:TOM1L2:GID4*	NA
GWAS catalog	Neutrophil count	156	15	1.15E-05	8.31E-04	*PLCL1:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:BRD3*	NA
GWAS catalog	Cholangiocarcinoma in primary sclerosing cholangitis (time to event)	14	5	1.76E-05	1.23E-03	*CACNA2D2:HEMK1:CISH:MAPKAPK3:DOCK3*	NA
GWAS catalog	Adventurousness	141	13	6.75E-05	4.54E-03	*DPF3:TCF4:LRP1B:KIF16B:SATB1:FOXP1:BANK1:SLC39A8:TET2:ATG10:SDK1:AUTS2:DGKI*	NA
GWAS catalog	Number of children ever born	5	3	1.59E-04	1.03E-02	*GATAD2B:EFNA5:FBXL17*	NA
GWAS catalog	Resting heart rate	138	12	2.22E-04	1.39E-02	*PPFIA2:SREBF1:BCL11A:PRKAR2A:QRICH1:LAMB2:KLHDC8B:DAG1:GMPPB:IP6K1:FAM212A:CSMD1*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GWAS catalog	Lentiform nucleus volume	6	3	3.12E-04	1.86E-02	*GATAD2B:DENND4B:SLC39A1*	NA
GWAS catalog	Cognitive ability	37	6	3.18E-04	1.86E-02	*SORCS3:EFTUD1:DCC:BCL11A:TET2:APBA1*	NA
GWAS catalog	Body fat distribution (trunk fat ratio)	236	16	3.90E-04	2.21E-02	*EFR3B:RFTN2:MARS2:BOLL:PLCL1:ARIH2OS:ARIH2:P4HTM:WDR6:DALRD3:NDUFAF3:IMPDH2:QRICH1:QARS:RBM6:DOCK3*	NA
GWAS catalog	Experiencing mood swings	40	6	4.93E-04	2.71E-02	*SERPINC1:DCC:TCF4:ARHGAP15:IP6K2:FBXL17*	NA
GWAS catalog	Hypersomnia (HLA-DQB1*06:02 negative)	7	3	5.36E-04	2.86E-02	*BCL11A:CRAT:PPP2R4*	NA
GWAS catalog	Broad depression or schizophrenia	16	4	5.98E-04	3.10E-02	*RTN1:BAG5:TCF4:SPATA31D1*	NA
GWAS catalog	Self-reported risk-taking behaviour	29	5	7.59E-04	3.66E-02	*TCF4:KHK:CGREF1:TBC1D5:TET2*	NA
GWAS catalog	Cognitive function	77	8	7.66E-04	3.66E-02	*CTNNA2:IP6K2:RHOA:TCTA:AMT:NICN1:BSN:CDKAL1*	NA
GWAS catalog	Percentage gas trapping	17	4	7.66E-04	3.66E-02	*SP1:DAND5:MACROD2:CSMD1*	NA
GWAS catalog	Estimated glomerular filtration rate	489	25	8.42E-04	3.92E-02	*GLMN:DLEU1:NFATC3:SLC7A6:MARVELD3:ZFHX3:DPEP1:CHMP1A:RP11-368I7.4:SLC6A4:MYO19:DHRS11:PITPNC1:FARSA:CALR:LRP1B:MACROD2:PLXNB1:DAG1:CACNA2D2:DOCK3:MANBA:CISD2:FBXL17:BRD3*	NA
GWAS catalog	Feeling fed-up	30	5	8.92E-04	4.05E-02	*FAM154B:DCC:TCF4:FAM117B:IP6K2*	NA
GWAS catalog	Red vs. brown/black hair color	18	4	9.65E-04	4.27E-02	*DPEP1:CHMP1A:CDK10:POMC*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
Chemical_and_Genetic_perturbation	HESSON_TUMOR_SUPPRESSOR_CLUSTER_3P21_3	8	8	1.70E-13	5.63E-10	*HYAL2:TUSC2:RASSF1:ZMYND10:NPRL2:CYB561D2:TMEM115:CACNA2D2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HESSON_TUMOR_SUPPRESSOR_CLUSTER_3P21_3
Chemical_and_Genetic_perturbation	MIKKELSEN_MEF_HCP_WITH_H3_UNMETHYLATED	224	20	1.33E-06	2.19E-03	*RIIAD1:KCNJ11:GPR182:DPEP3:FAM178B:SPAG16:DND1:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA9:PCDHA10:PCDHA11:PCDHA13:PCDHAC1:HTR5A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/MIKKELSEN_MEF_HCP_WITH_H3_UNMETHYLATED
Immunologic_signatures	GSE2770_IL12_AND_TGFB_VS_IL4_TREATED_ACT_CD4_TCELL_48H_UP	199	18	3.72E-06	1.81E-02	*NUCB2:STAT6:DNAJA4:FAM65A:ESRP2:CDK10:TOM1L2:TCF4:ANKRD44:COQ10B:RFTN2:USP4:APEH:RNF123:IP6K1:PPP3CA:APBB3:TAPBP*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GSE2770_IL12_AND_TGFB_VS_IL4_TREATED_ACT_CD4_TCELL_48H_UP
Positional_gene_sets	chr3p21	202	75	2.71E-67	8.11E-65	*FBXW12:PLXNB1:CCDC51:TMA7:ATRIP:TREX1:SHISA5:PFKFB4:UCN2:COL7A1:UQCRC1:TMEM89:SLC26A6:CELSR3:NCKIPSD:IP6K2:PRKAR2A:SLC25A20:ARIH2OS:ARIH2:P4HTM:WDR6:DALRD3:NDUFAF3:IMPDH2:QRICH1:QARS:USP19:LAMB2:CCDC71:KLHDC8B:CCDC36:USP4:GPX1:RHOA:TCTA:AMT:NICN1:DAG1:BSN:APEH:MST1:RNF123:AMIGO3:GMPPB:IP6K1:CDHR4:FAM212A:UBA7:TRAIP:CAMKV:MST1R:MON1A:RBM6:RBM5:SEMA3F:GNAT1:GNAI2:LSMEM2:IFRD2:HYAL3:NAT6:HYAL1:HYAL2:TUSC2:RASSF1:ZMYND10:NPRL2:CYB561D2:TMEM115:CACNA2D2:HEMK1:CISH:MAPKAPK3:DOCK3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr3p21
Positional_gene_sets	chr16q22	120	47	1.58E-43	2.37E-41	*LRRC36:TPPP3:ZDHHC1:HSD11B2:ATP6V0D1:AGRP:FAM65A:CTCF:RLTPR:ACD:PARD6A:ENKD1:GFOD2:RANBP10:TSNAXIP1:CENPT:THAP11:NU*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr16q22

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						TF2:EDC4:NRN1L:PSKH1:CTRL:PSMB10:LCAT:SLC12A4:DPEP3:DPEP2:DUS2:DDX28:NFATC3:ESRP2:PLA2G15:SLC7A6:SLC7A6OS:PRMT7:SMPD3:ZNF23:ZNF19:CHST4:TAT:MARVELD3:PHLPP2:AP1G1:ATXN1L:IST1:ZNF821:ZFHX3	
Positional_gene_sets	chr5q31	186	31	8.17E-17	8.15E-15	*SLC4A9:ANKHD1:ANKHD1-EIF4EBP3:SRA1:EIF4EBP3:APBB3:SLC35A4:CD14:NDUFA2:TMCO6:IK:WDR55:DND1:HARS:HARS2:ZMAT2:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr5q31
Positional_gene_sets	chr4q24	23	12	7.02E-14	5.24E-12	*PPP3CA:BANK1:SLC39A8:MANBA:UBE2D3:CISD2:SLC9B1:SLC9B2:BDH2:CENPE:TET2:PPA2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr4q24
Positional_gene_sets	chr12q13	265	24	8.94E-08	5.35E-06	*RARG:MFSD5:ESPL1:PFDN5:AAAS:SP7:SP1:AMHR2:PRR13:PCBP2:MAP3K12:TARBP2:NPFF:ATF7:ATP5G2:SDR9C7:RDH16:GPR182:ZBTB39:TAC3:MYO1A:TMEM194A:NAB2:STAT6*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr12q13
Positional_gene_sets	chr1q25	76	12	4.71E-07	2.35E-05	*PRDX6:SLC9C2:ANKRD45:KLHL20:CENPL:DARS2:ZBTB37:SERPINC1:RC3H1:RABGAP1L:GPR52:BRINP2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr1q25
Positional_gene_sets	chr2q33	81	12	9.57E-07	4.09E-05	*ANKRD44:SF3B1:COQ10B:HSPD1:HSPE1:HSPE1-MOB4:MOB4:RFTN2:MARS2:BOLL:PLCL1:FAM117B*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr2q33
Positional_gene_sets	chr2p23	93	12	4.27E-06	1.60E-04	*EFR3B:POMC:SLC35F6:CENPA:DPYSL5:MAPRE3:TMEM214:AGBL5:OST4:EMILIN1:KHK:CGREF1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr2p23
Positional_gene_sets	chr7p13	31	7	1.05E-05	3.47E-04	*DDX56:TMED4:OGDH:ZMIZ2:PPIA:H2AFV:PURB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr7p13

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
Positional_gene_sets	chr15q25	73	10	1.58E-05	4.71E-04	*ACSBG1:DNAJA4:WDR61:EFTUD1:FAM154B:GOLGA6L10:GOLGA6L9:RPS17:GOLGA6L18:GOLGA6L20:RPS17L:CPEB1:AP3B2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr15q25
Positional_gene_sets	chr17q11	79	10	3.19E-05	8.67E-04	*TAOK1:ABHD15:TP53I13:GIT1:ANKRD13B:CORO6:SSH2:EFCAB5:NSRP1:SLC6A4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr17q11
Positional_gene_sets	chr22q12	114	12	3.49E-05	8.70E-04	*PITPNB:TTC28:CHEK2:HSCB:CCDC117:XBP1:ZNRF3:SMTN:SELM:INPP5J:PLA2G3:LARGE*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr22q12
Positional_gene_sets	chr17p11	70	8	4.01E-04	9.23E-03	*RAI1:SREBF1:TOM1L2:LRRC48:ATPAF2:GID4:DRG2:MYO15A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr17p11
Positional_gene_sets	chr1q21	218	15	5.04E-04	1.08E-02	*SNX27:CELF3:RIIAD1:GATAD2B:DENND4B:CRTC2:SLC39A1:CREB3L4:JTB:RAB13:RPS27:NUP210L:TPM3:UBAP2L:KCNN3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr1q21
Positional_gene_sets	chr4q31	67	7	1.57E-03	3.13E-02	*CCRN4L:ELF2:MGARP:NDUFC1:NAA15:RAB33B:MAML3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr4q31
Positional_gene_sets	chr2q22	11	3	2.34E-03	4.37E-02	*LRP1B:ARHGAP15:GTDC1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr2q22
Curated_gene_sets	HESSON_TUMOR_SUPPRESSOR_CLUSTER_3P21_3	8	8	1.70E-13	9.37E-10	*HYAL2:TUSC2:RASSF1:ZMYND10:NPRL2:CYB561D2:TMEM115:CACNA2D2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HESSON_TUMOR_SUPPRESSOR_CLUSTER_3P21_3
Curated_gene_sets	MIKKELSEN_MEF_HCP_WITH_H3_UNMETHYLATED	224	20	1.33E-06	3.65E-03	*RIIAD1:KCNJ11:GPR182:DPEP3:FAM178B:SPAG16:DND1:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA9:PCDHA10:PCDHA11:PCDHA13:PCDHAC1:HTR5A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/MIKKELSEN_MEF_HCP_WITH_H3_UNMETHYLATED

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
KEGG	KEGG_AXON_GUIDANCE	128	12	1.09E-04	2.02E-02	*CDC42:NFATC3:DCC:DPYSL5:PPP3R1:SEMA4C:PLXNB1:RHOA:SEMA3F:GNAI2:PPP3CA:EFNA5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/KEGG_AXON_GUIDANCE
microRNA_targets	TCTCTCC_MIR185	123	26	6.27E-17	1.39E-14	*CDC42:KCNN3:NFATC3:PHLPP2:PITPNC1:EMC10:PRKAR2A:RHOA:BSN:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:SYNGAP1:APBA1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TCTCTCC_MIR185
microRNA_targets	ACCAATC_MIR509	48	17	1.29E-15	1.42E-13	*PHLPP2:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PURB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ACCAATC_MIR509
microRNA_targets	AGGGCAG_MIR18A	138	24	9.94E-14	7.32E-12	*SNX27:ATF7:ZFYVE1:SMPD3:UBE2Z:PFKFB4:DAG1:CAMKV:TET2:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AGGGCAG_MIR18A
microRNA_targets	ATGTAGC_MIR221_MIR222	140	24	1.38E-13	7.64E-12	*KLC1:CTCF:PPP3R1:AGFG1:KIF16B:GNAI2:IGF2BP2:ANKHD1:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATGTAGC_MIR221_MIR222
microRNA_targets	CAGCACT_MIR5123P	154	23	8.79E-12	3.88E-10	*RARG:PPFIA2:ESRP2:IP6K1:TUSC2:DOCK3:PPP3CA:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PURB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CAGCACT_MIR5123P
microRNA_targets	GTTTGTT_MIR495	255	28	9.27E-11	3.42E-09	*SP1:NAB2:AP1G1:CDH13:UBE2Z:AGBL5:BCL11A:LARGE:SATB1:DAG1:PPP3CA:MAML3:GPM6A:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCD*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GTTTGTT_MIR495

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						HA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2	
microRNA_targets	CAGCTTT_MIR320	255	27	4.59E-10	1.45E-08	*TPM3:TAC3:CPEB1:NSRP1:FAM117B:DAG1:UBE2D3:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PHF1:PURB:CALN1:CALD1:FAM49B*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CAGCTTT_MIR320
microRNA_targets	GTATTAT_MIR3693P	207	23	3.58E-09	9.90E-08	*RAI1:LRP1B:MOB4:BOLL:UBE2D3:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PAXIP1:ZFPM2:DNAJB5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GTATTAT_MIR3693P
microRNA_targets	TAATAAT_MIR126	219	23	1.06E-08	2.50E-07	*SP7:TBC1D15:AP1G1:TAOK1:NDUFAF3:GMPPB:ALCAM:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PURB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TAATAAT_MIR126
microRNA_targets	CACTTTG_MIR520G_MIR520H	238	24	1.13E-08	2.50E-07	*NPAS3:EFTUD1:DPYSL5:SEMA4C:CELSR3:PRKAR2A:PPP3CA:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:CALU:DNAJB5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CACTTTG_MIR520G_MIR520H
microRNA_targets	GGTGTGT_MIR329	113	16	2.90E-08	5.73E-07	*NAA15:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GGTGTGT_MIR329
microRNA_targets	ATTCTTT_MIR186	270	25	3.11E-08	5.73E-07	*CDC42:SNX27:BRINP2:ZBTB39:SMPD3:GTDC1:PFKFB4:IGF2BP2:NAA15:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PURB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATTCTTT_MIR186

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
microRNA_targets	TTTGCAC_MIR19A_MIR19B	512	36	4.51E-08	7.66E-07	*SNX27:KLHL20:ADIPOR2:MAP3K12:RTN1:GRIN2A:ESRP2:AP1G1:DPYSL5:SEMA4C:ARIH2:DAG1:BSN:RASSF1:DOCK3:FOXP1:CCRN4L:RAB33B:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:CSMD1:LONRF1:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TTTGCAC_MIR19A_MIR19B
microRNA_targets	TGCTTTG_MIR330	329	27	1.08E-07	1.70E-06	*CELF3:GATAD2B:TPM3:RC3H1:PRKG1:NFATC3:PHLPP2:LRP1B:MACROD2:DAG1:GPM6A:FBXL17:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGCTTTG_MIR330
microRNA_targets	AAGCACA_MIR218	400	30	1.55E-07	2.28E-06	*SLC39A1:PRKG1:ADIPOR2:SP1:NUMB:RANBP10:ANKRD13B:NFIX:GNAI2:GPM6A:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:ZMIZ2:PURB:STXBP1:DOLPP1:PPP2R4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AAGCACA_MIR218
microRNA_targets	AGCACTT_MIR93_MIR302A_MIR302B_MIR302C_MIR302D_MIR372_MIR373_MIR520E_MIR520A_MIR526B_MIR520B_MIR520C_MIR520D	343	27	2.50E-07	3.45E-06	*GATAD2B:CRTC2:NPAS3:PHLPP2:DPYSL5:BCL11A:PPP3R1:IP6K1:TUSC2:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:ZBTB9:PURB:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AGCACTT_MIR93_MIR302A_MIR302B_MIR302C_MIR302D_MIR372_MIR373_MIR520E_MIR520A_MIR526B_MIR520B_MIR520C_MIR520D
microRNA_targets	TGAATGT_MIR181A_MIR181B_MIR181C_MIR181D	485	32	1.04E-06	1.35E-05	*WSCD2:GOLGA6L9:GOLGA6L20:AP1G1:CDH13:GID4:BCL11A:PPP3R1:SEMA4C:AGFG1:PLCL2:CACNA2D2:FOXP1:IGF2BP2:NAA15:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGAATGT_MIR181A_MIR181B_MIR181C_MIR181D

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						12:PCDHA13:PCDHAC1:PCDHAC2:NKAIN2:PURB:LONRF1	
microRNA_targets	TGCACTT_MIR519C_MIR519B_MIR519A	442	30	1.28E-06	1.57E-05	*GATAD2B:KLHL20:ADIPOR2:MAP3K12:RTN1:EFTUD1:ZDHHC1:SSH2:NFIX:MAPRE3:MACROD2:PPP3CA:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PURB:CALD1:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGCACTT_MIR519C_MIR519B_MIR519A
microRNA_targets	GCACTTT_MIR175P_MIR20A_MIR106A_MIR106B_MIR20B_MIR519D	592	36	1.51E-06	1.69E-05	*GATAD2B:KLHL20:MAP3K12:NPAS3:EFTUD1:ZDHHC1:PHLPP2:GID4:SSH2:DPYSL5:MAPRE3:PPP3R1:FAM117B:IP6K1:TUSC2:PPP3CA:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:PHF1:ZBTB9:PURB:CALD1:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GCACTTT_MIR175P_MIR20A_MIR106A_MIR106B_MIR20B_MIR519D
microRNA_targets	TGGTGCT_MIR29A_MIR29B_MIR29C	518	33	1.53E-06	1.69E-05	*CDC42:SP1:PPP1R13B:SMPD3:AP1G1:GID4:ANKRD13B:CORO6:ATP5G1:NFIX:BCL11A:CCDC117:COL7A1:DAG1:ELF2:NREP:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:CALU:DOLPP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGGTGCT_MIR29A_MIR29B_MIR29C
microRNA_targets	TGCTGCT_MIR15A_MIR16_MIR15B_MIR195_MIR424_MIR497	602	35	5.71E-06	6.01E-05	*CDC42:ZBTB39:BAG5:ACSBG1:TPPP3:PSKH1:NFATC3:PLA2G15:PHLPP2:ANKRD13B:SLC6A4:LRP1B:MOB4:INPP5J:CAMKV:RBM6:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:ZBTB9:PURB:STXBP1:DOLPP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGCTGCT_MIR15A_MIR16_MIR15B_MIR195_MIR424_MIR497
microRNA_targets	CCCACAT_MIR2993P	53	9	6.98E-06	7.01E-05	*CDC42:AP1G1:GIT1:TCF4:MAPRE3:AGBL5:BCL11A:APBB3:PAXIP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CCCACAT_MIR2993P

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
microRNA_targets	GTGCCTT_MIR506	723	39	9.70E-06	9.32E-05	*EVI5:RARG:SP7:SP1:PRKD1:PSEN1:CPEB1:RANBP10:PSKH1:SMPD3:AP1G1:SSH2:SNF8:NFIX:EMC10:BCL11A:KIF16B:GNAI2:NAA15:NSUN2:SLC35A4:PCDHA1:PCDHA2:PCDHA3:PCDHA4:PCDHA5:PCDHA6:PCDHA7:PCDHA8:PCDHA9:PCDHA10:PCDHA11:PCDHA12:PCDHA13:PCDHAC1:PCDHAC2:CALU:FAM129B:CRAT*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GTGCCTT_MIR506
microRNA_targets	GAGCTGG_MIR337	161	13	2.57E-04	2.37E-03	*SNX27:STIP1:SP7:RANBP10:GIT1:XBP1:USP19:CAMKV:FBXL17:DGKI:DNAJB5:VCP:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GAGCTGG_MIR337
microRNA_targets	TCTGATA_MIR361	90	8	2.12E-03	1.87E-02	*SP1:RAD23A:LRP1B:RHOA:DAG1:DOCK3:SDK1:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TCTGATA_MIR361
microRNA_targets	GGCAGCT_MIR22	228	14	2.26E-03	1.92E-02	*SP1:MAP3K12:ZBTB39:CPEB1:AGBL5:BOLL:IP6K1:FOXP1:TET2:PURB:DGKI:FAM49B:DNAJB5:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GGCAGCT_MIR22
microRNA_targets	CTACTGT_MIR199A	181	12	2.43E-03	1.93E-02	*CDC42:SORCS3:STAT6:RBM25:GOLGA6L9:GOLGA6L20:SLC7A6:PHLPP2:AP1G1:FOXP1:NAA15:GPM6A:DGKI*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CTACTGT_MIR199A
microRNA_targets	CTGAGCC_MIR24	230	14	2.45E-03	1.93E-02	*MAPK8IP1:RARG:SP1:RANBP10:CENPT:PSKH1:TAOK1:SSH2:PLCL2:IP6K2:BSN:DOCK3:RGL2:APBA1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CTGAGCC_MIR24
microRNA_targets	ACTTTAT_MIR1425P	285	16	2.81E-03	2.15E-02	*RC3H1:NUDT22:PCBP2:GCH1:RTN1:ZFYVE21:AP1G1:SREBF1:SSH2:LRP1B:RHOA:ALCAM:APBB3:ZFPM2:ELAVL2:FAM129B*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ACTTTAT_MIR1425P
microRNA_targets	ATAAGCT_MIR21	117	9	3.10E-03	2.28E-02	*GATAD2B:PCBP2:GID4:BOLL:SATB1:PPP3CA:UBE2D3:ELF2:PURB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATAAGCT_MIR21
microRNA_targets	ACATTCC_MIR1_MIR206	298	16	4.34E-03	3.09E-02	*CDC42:TPM3:TBC1D15:GCH1:WDR61:CPEB1:SLC7A6:PHLPP2:AP1G1:GIT1:HSPD1:CELSR3:IP6K2:WDR6:BSN:FOXP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ACATTCC_MIR1_MIR206

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
microRNA_targets	TTCCGTT_MIR191	29	4	6.00E-03	4.15E-02	*MAP3K12:AP1G1:MAPRE3:FOXP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TTCCGTT_MIR191
TF_targets	SYATTGTG_UNKNOWN	229	19	7.13E-06	4.35E-03	*TPM3:RTN1:BAG5:APOPT1:RANBP10:TSNAXIP1:THAP11:BCL11A:CTNNA2:UCN2:CELSR3:BSN:MON1A:IFRD2:FOXP1:GPM6A:ANKHD1:ANKHD1-EIF4EBP3:ADAM22*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SYATTGTG_UNKNOWN
TF_targets	SREBP_Q3	258	19	3.80E-05	1.16E-02	*AMHR2:NSRP1:SLC6A4:GGNBP2:BCL11A:PLA2G3:IP6K2:DALRD3:NDUFAF3:QRICH1:RHOA:MST1:RNF123:HYAL1:APBB3:SLC35A4:DNAJB5:TTC16:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SREBP_Q3
TF_targets	CP2_02	253	18	9.42E-05	1.91E-02	*FKBP2:PPFIA2:RTN1:TPPP3:ENKD1:ANKRD13B:CORO6:MAPRE3:MACROD2:TBC1D5:DALRD3:NDUFAF3:GMPPB:CAMKV:RASSF1:CUTA:CALD1:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CP2_02
TF_targets	GATTGGY_NFY_Q6_01	1167	51	1.25E-04	1.91E-02	*SLC9C2:PEX16:STIP1:MLF2:ESPL1:SP1:ATP5G2:TAC3:DLEU1:DPF3:NUMB:XRCC3:ZFYVE21:PARD6A:IST1:ABHD15:TP53I13:ZNHIT3:GGNBP2:ATP5G1:DPYSL5:TANK:COQ10B:HSCB:XBP1:PLA2G3:CCDC51:TMA7:TREX1:SLC26A6:CELSR3:DALRD3:NDUFAF3:RHOA:TCTA:GMPPB:GNAI2:CISH:UBE2D3:EFNA5:ZBTB22:DAXX:CUTA:OGDH:CALU:ELAVL2:DNAJB5:VCP:CLTA:DOLPP1:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GATTGGY_NFY_Q6_01
TF_targets	SREBP1_Q6	245	17	1.97E-04	2.41E-02	*KCNN3:PEX16:RARG:STAT6:ZFYVE1:TAOK1:NFIX:SMTN:PLA2G3:DALRD3:NDUFAF3:IMPDH2:RHOA:HYAL1:MAPKAPK3:MAML3:ZBTB9*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SREBP1_Q6
TF_targets	P300_01	254	17	3.02E-04	2.55E-02	*WNT4:KCNN3:RARG:DPF3:SLC12A4:SMPD3:ZNF23:GGNBP2:BCL11A:SEMA4C:DALRD3:NDUFAF3:FOXP1:PPP3CA:MAML3:PCDHAC2:ZBTB9*	http://www.gsea-msigdb.org/gsea/msigdb/cards/P300_01

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
TF_targets	DR1_Q3	259	17	3.78E-04	2.55E-02	*CELF3:TRPT1:NUDT22:DPF3:PAPLN:TOM1L2:LRRC48:SSH2:MLTK:HSPD1:HSPE1:SMTN:SELM:SATB1:TREX1:CUTA:TMED4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/DR1_Q3
TF_targets	CGTSACG_PAX3_B	147	12	3.98E-04	2.55E-02	*MFSD5:NAB2:CTCF:NSRP1:JOSD2:BCL11A:XBP1:ANKHD1:ANKHD1-EIF4EBP3:SLC25A40:DBF4:STXBP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CGTSACG_PAX3_B
TF_targets	WTTGKCTG_UNKNOWN	519	27	4.05E-04	2.55E-02	*PEX16:MACROD1:SP7:PPFIA2:DLEU1:GFOD2:RANBP10:TSNAXIP1:IST1:GGNBP2:PITPNC1:TCF4:DPYSL5:SEMA4C:TANK:COQ10B:MACROD2:PLA2G3:IMPDH2:FOXP1:MAML3:PHF1:ZBTB9:POU6F2:CALU:CALD1:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/WTTGKCTG_UNKNOWN
TF_targets	PAX2_02	263	17	4.51E-04	2.55E-02	*DNAJC4:SP7:ATP5G2:RTN1:DPF3:MARVELD3:TCF4:IP6K2:GPX1:RHOA:TCTA:IFRD2:CACNA2D2:PPP3CA:MAML3:RGL2:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/PAX2_02
TF_targets	AP4_01	265	17	4.91E-04	2.55E-02	*MAPK8IP1:PFDN5:PCBP2:NAB2:TPPP3:NUTF2:ESRP2:CDH13:MAPRE3:BCL11A:SEMA4C:DALRD3:NDUFAF3:HYAL2:FOXP1:DNAJB5:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AP4_01
TF_targets	SCGGAAGY_ELK1_02	1241	51	5.34E-04	2.55E-02	*GFI1:TPM3:PEX16:TRPT1:NUDT22:VEGFB:MFSD5:PCBP2:EFTUD1:THAP11:NUTF2:EDC4:ZNF23:MYO19:PIGW:MRM1:UBE2Z:SNF8:RAD23A:JOSD2:SLC35F6:SF3B1:MED15:TBC1D5:SLC25A20:NDUFAF3:CCDC71:RHOA:TCTA:APEH:SEMA3F:NPRL2:CYB561D2:NSUN2:EFNA5:ANKHD1:ANKHD1-EIF4EBP3:WDR55:HARS:HARS2:VPS52:RPS18:B3GALT4:WDR46:PFDN6:ZBTB9:PURB:CALU:ELAVL2:DNAJB5:PIGO*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SCGGAAGY_ELK1_02
TF_targets	IK2_01	269	17	5.82E-04	2.55E-02	*WNT4:STIP1:SP7:PPFIA2:ATP6V0D1:TTLL6:AGBL5:BCL11A:SLC26A6:DALRD3:NDUFAF3:SEMA3F:NAA15:GPM6A:TMCO6:CALU:ZFPM2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/IK2_01

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
TF_targets	HFH1_01	246	16	6.14E-04	2.55E-02	*ZBTB37:PIK3C2A:ZFYVE1:BCL11A:RFTN2:CCDC117:IP6K2:IMPDH2:GPX1:DOCK3:SLC39A8:EFNA5:WDR46:PFDN6:ZBTB22:ELAVL2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HFH1_01
TF_targets	MYOD_Q6	247	16	6.42E-04	2.55E-02	*KCNN3:DPF3:HSD11B2:ESRP2:SSH2:SEMA4C:GTDC1:NCKIPSD:DALRD3:NDUFAF3:NAA15:ANKHD1:ANKHD1-EIF4EBP3:NKAIN2:CRAT:PPP2R4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/MYOD_Q6
TF_targets	TGGAAA_NFAT_Q4_01	1899	71	6.70E-04	2.55E-02	*WNT4:GFI1:CELF3:NUP210L:TPM3:ZBTB37:SERPINC1:RABGAP1L:PEX16:STIP1:VEGFB:RARG:SP1:PCBP2:NAB2:PPFIA2:DPF3:NUMB:PPP1R13B:EDC4:NRN1L:SMPD3:AP1G1:NSRP1:MYO19:PIGW:TTLL6:ATP5G1:PITPNC1:TCF4:RAD23A:NFIX:POMC:BCL11A:SEMA4C:LRP1B:RFTN2:PLCL1:XBP1:PLXNB1:TREX1:IP6K2:ARIH2:CCDC71:GPX1:RHOA:TCTA:BSN:CAMKV:HYAL3:NAT6:HYAL2:CISH:DOCK3:FOXP1:NDUFC1:MAML3:NREP:ANKHD1:ANKHD1-EIF4EBP3:PCDHA6:PCDHA11:PCDHA13:RGL2:AUTS2:CALU:CALD1:VCP:APBA1:STXBP1:CRAT*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGGAAA_NFAT_Q4_01
TF_targets	GGGTGGRR_PAX4_03	1297	52	8.25E-04	2.93E-02	*TPM3:KCNN3:ZBTB37:RARG:MFSD5:SP7:ATF7:NAB2:STAT6:PPFIA2:GCH1:ZFYVE1:TPPP3:FAM65A:CTCF:SLC12A4:AP1G1:ZNF821:TAOK1:ANKRD13B:DHRS11:UBE2Z:PITPNC1:TCF4:RAD23A:NFIX:JOSD2:DPYSL5:MAPRE3:AGBL5:EMILIN1:SEMA4C:HSCB:IMPDH2:LAMB2:CCDC71:RHOA:TCTA:GMPPB:GNAI2:HYAL1:HYAL2:UBE2D3:NAA15:NREP:PHF1:ZBTB9:OGDH:AUTS2:ZFPM2:ELAVL2:APBA1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GGGTGGRR_PAX4_03
TF_targets	RTAAACA_FREAC2_01	927	40	8.66E-04	2.93E-02	*CRTC2:RPS27:KCNN3:PRDX6:ZBTB37:RABGAP1L:PIK3C2A:RARG:ATF7:STAT6:ZFYVE1:FAM65A:CTCF:NRN1L:NFATC3:TTLL6:PITPNC1:TCF4:NFIX:BCL11A:SLC26A6:IP6K2:IMPDH2:GPX1:DOCK3:PP*	http://www.gsea-msigdb.org/gsea/msigdb/cards/RTAAACA_FREAC2_01

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
						P3CA:TET2:NAA15:MAML3:GPM6A:HARS:HARS2:PCDHA4:WDR46:PFDN6:ZBTB22:ABCB1:CALD1:LONRF1:RP1	
TF_targets	TTCYRGAA_UNKNOWN	334	19	1.02E-03	3.26E-02	*CELF3:PRDX6:FLRT1:STIP1:RTN1:DCAF4:NFATC3:MYO19:PIGW:HSPD1:HSPE1:RFTN2:CCDC117:GPX1:NPY2R:VPS52:RPS18:DNAJB5:VCP*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TTCYRGAA_UNKNOWN
TF_targets	NFY_01	260	16	1.11E-03	3.28E-02	*GLB1L2:DLEU1:DPF3:NUMB:GGNBP2:COQ10B:FAM117B:HSCB:PLA2G3:CCDC51:TMA7:TREX1:GNAT1:DND1:VCP:CLTA*	http://www.gsea-msigdb.org/gsea/msigdb/cards/NFY_01
TF_targets	HNF4_DR1_Q3	261	16	1.15E-03	3.28E-02	*PEX16:TRPT1:NUDT22:DPF3:PAPLN:LCAT:TOM1L2:LRRC48:MLTK:HSPD1:HSPE1:SELM:TREX1:SLC26A6:IP6K2:CUTA*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HNF4_DR1_Q3
TF_targets	GATA1_01	237	15	1.18E-03	3.28E-02	*RARG:SP7:NAB2:GRIN2A:CTCF:JOSD2:MAPRE3:DALRD3:NDUFAF3:RBM5:MAML3:RGL2:ELAVL2:CLTA:DOLPP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GATA1_01
TF_targets	NFY_Q6_01	265	16	1.35E-03	3.58E-02	*GLB1L2:RANBP10:TSNAXIP1:GGNBP2:DPYSL5:HSCB:PLA2G3:CCDC51:TMA7:CELSR3:RHOA:TCTA:GNAI2:DAXX:VCP:DOLPP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/NFY_Q6_01
TF_targets	E2A_Q2	243	15	1.52E-03	3.84E-02	*GYLTL1B:MACROD1:LRRC36:TPPP3:ESRP2:ANKRD13B:GGNBP2:JSRP1:FBXL17:ANKHD1:ANKHD1-EIF4EBP3:NKAIN2:DNAJB5:CRAT:PPP2R4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/E2A_Q2
TF_targets	HNF4ALPHA_Q6	269	16	1.57E-03	3.84E-02	*GPR52:PEX16:MLF2:ZFYVE1:PAPLN:NUTF2:ESRP2:SSH2:MLTK:SATB1:SLC26A6:CCDC71:DOCK3:CUTA:PPIA:IER5L*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HNF4ALPHA_Q6
TF_targets	COUP_DR1_Q6	248	15	1.85E-03	4.35E-02	*CELF3:PEX16:DPF3:PAPLN:LCAT:TOM1L2:LRRC48:HSPD1:HSPE1:TREX1:SHISA5:SLC26A6:CCDC71:UBE2D3:CUTA*	http://www.gsea-msigdb.org/gsea/msigdb/cards/COUP_DR1_Q6
TF_targets	YY1_01	249	15	1.93E-03	4.35E-02	*TPM3:ATP5G2:CTCF:AP1G1:IST1:SSH2:TCF4:MLTK:PLXNB1:IP6K2:RHOA:TCTA:GNAI2:CUTA:CALD1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/YY1_01

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
TF_targets	GCTNWTTGK_UNKNOWN	303	17	2.12E-03	4.51E-02	*NUCB2:ESPL1:LRRC36:SSH2:SLC6A4:GGNBP2:HSCB:PLA2G3:IP6K2:CCDC71:NREP:ANKHD1:ANKHD1-EIF4EBP3:H2AFV:CALD1:VCP:TTC16*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GCTNWTTGK_UNKNOWN
TF_targets	TTCNRGNNNNTTC_HSF_Q6	155	11	2.14E-03	4.51E-02	*ZBTB37:STIP1:RTN1:NUTF2:NFATC3:JOSD2:HSPD1:HSPE1:RBM6:FOXP1:DNAJB5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TTCNRGNNNNTTC_HSF_Q6
TF_targets	RCGCANGCGY_NRF1_Q6	947	39	2.31E-03	4.71E-02	*SORCS3:PEX16:FKBP2:ATP5G2:TBC1D15:WDHD1:ATP6V0D1:CTCF:THAP11:ESRP2:CDK10:ABHD15:TP53I13:SSH2:EMC10:MAPRE3:HSPD1:HSPE1:MACROD2:TBC1D5:UQCRC1:PRKAR2A:RHOA:TCTA:BSN:MST1:RNF123:RASSF1:ZMYND10:NPRL2:CYB561D2:TMEM115:UBE2D3:NAA15:RPS23:APBB3:SLC35A4:PHF1:TMED4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/RCGCANGCGY_NRF1_Q6
TF_targets	AAAYWAACM_HFH4_01	255	15	2.42E-03	4.77E-02	*ZBTB37:PIK3C2A:MAPK8IP1:TCF4:NFIX:RFTN2:GPX1:DOCK3:SLC39A8:NREP:RGL2:CUTA:NKAIN2:H2AFV:CALD1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AAAYWAACM_HFH4_01

Supplementary Table 5. 11: Gene-set Analysis Results for Unique Loci Jointly Associated with Cognitive Factor 3 and Schizophrenia

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GO_bp	GO_REGULATION_OF_NEURON_DIFFERENTIATION	633	18	9.25E-06	4.22E-02	*ZNF365:CPEB3:MOB2:MARK2:SEMA6D:CRK:DLG4:DVL2:TCF4:SYT3:NGEF:CNTN4:ROBO2:NCK1:EFNA5:BAI3:ASAP1:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_REGULATION_OF_NEURON_DIFFERENTIATION
GO_bp	GO_REGULATION_OF_RELAXATION_OF_CARDIAC_MUSCLE	6	3	1.23E-05	4.22E-02	*PDE4B:HRC:PDE4D*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_REGULATION_OF_RELAXATION_OF_CARDIAC_MUSCLE
GO_bp	GO_REGULATION_OF_NEURON_PROJECTION_DEVELOPMENT	478	15	1.72E-05	4.22E-02	*ZNF365:CPEB3:MOB2:MARK2:SEMA6D:CRK:DLG4:DVL2:SYT3:NGEF:ROBO2:NCK1:EFNA5:BAI3:ASAP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_REGULATION_OF_NEURON_PROJECTION_DEVELOPMENT
GWAS catalog	Schizophrenia	727	37	1.16E-18	2.11E-15	*SLC45A1:RERE:ELAVL4:PDE4B:CEP170:SDCCAG8:PRKG1:ZNF365:PCNX:HYKK:PSMA4:CHRNA5:CORO7-PAM16:CORO7:DNAJA3:NMRAL1:CDIP1:CDH13:YWHAE:TCF4:CTDP1:GIGYF2:KCNJ13:NGEF:CNTN4:RBMS3:FOXP1:PPP2R3A:MSL2:PCCB:STAG1:SLC35G2:NCK1:SNAP91:FUT9:FAM184A:IMMP2L*	NA
GWAS catalog	Cognitive ability, years of educational attainment or schizophrenia (pleiotropy)	165	16	9.91E-13	8.99E-10	*SDCCAG8:ZNF365:PCDH17:PCNX:SEMA6D:CDH13:TCF4:HAT1:GIGYF2:CNTN4:FOXP1:STAG1:EFNA5:SNAP91:FUT9:IMMP2L*	NA
GWAS catalog	Cognitive function	77	12	2.52E-12	1.53E-09	*PCDH17:HS6ST3:RNF43:HSF5:MTMR4:SEPT4:TEX14:RAD51C:PPM1E:TRIM37:SKA2:PDE4D*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GWAS catalog	Autism spectrum disorder or schizophrenia	612	22	1.51E-08	5.60E-06	*SLC45A1:RERE:PRKG1:PCNX:HYKK:PSMA4:CHRNA5:TCF4:GIGYF2:KCNJ13:NGEF:CNTN4:FOXP1:PPP2R3A:MSL2:PCCB:STAG1:SLC35G2:NCK1:PRSS35:SNAP91:IMMP2L*	NA
GWAS catalog	Post bronchodilator FEV1/FVC ratio	196	13	1.54E-08	5.60E-06	*SEMA6D:HYKK:PSMA4:CHRNA5:SLCO3A1:CDH13:PPM1E:TCF4:GULP1:CNTN4:ROBO2:PDE4D:BRINP1*	NA
GWAS catalog	Depression	57	7	5.70E-07	1.72E-04	*SLC45A1:RERE:RBFOX1:MYO18A:CRYBA1:NUFIP2:TCF4*	NA
GWAS catalog	Mental health study participation (completed survey)	27	5	3.09E-06	8.01E-04	*CEP170:SDCCAG8:RBFOX1:SUPT4H1:TCF4*	NA
GWAS catalog	Smoking status (ever vs never smokers)	187	10	5.21E-06	1.11E-03	*RERE:ELAVL4:PDE4B:METTL15:HS6ST3:SEMA6D:OLA1:EFNA5:CADPS2:BRINP1*	NA
GWAS catalog	Chronotype	549	17	5.49E-06	1.11E-03	*PDE4B:ZNF365:CPEB3:METTL15:MYO16:TEX29:SEMA6D:RBFOX1:TEX14:TCF4:CNTN4:FOXP1:ROBO2:PDE4D:EFNA5:STK31:RORB*	NA
GWAS catalog	General risk tolerance (MTAG)	247	11	1.01E-05	1.83E-03	*SDCCAG8:METTL15:SEMA6D:RBFOX1:CDH13:ARHGAP28:TCF4:FOXP1:STAG1:BAI3:CADPS2*	NA
GWAS catalog	Waist-to-hip ratio adjusted for BMI (additive genetic model)	60	6	1.27E-05	2.10E-03	*CLSPN:DNAH10:CCDC92:UGGT2:CORO7:DNAJA3*	NA
GWAS catalog	Reaction time	39	5	2.03E-05	2.90E-03	*AGBL4:NMNAT2:YWHAE:METAP1D:OLA1*	NA
GWAS catalog	Atrial fibrillation	219	10	2.07E-05	2.90E-03	*AGBL4:DNAH10:CCDC92:MYO1E:YWHAE:CRK:MYO1C:PPP2R3A:EFNA5:SLIT3*	NA

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GWAS catalog	Response to radiotherapy in cancer (late toxicity)	8	3	3.40E-05	4.41E-03	*SEMA6D:RBMS3:CNTNAP2*	NA
GWAS catalog	Erectile dysfunction	48	5	5.66E-05	6.85E-03	*CORO7:DNAJA3:NMRAL1:HMOX2:CDH13*	NA
GWAS catalog	Testicular germ cell tumor	79	6	6.16E-05	6.99E-03	*SEPT4:TEX14:RAD51C:PPM1E:TRIM37:SKA2*	NA
GWAS catalog	Gut microbiota (bacterial taxa)	55	5	1.10E-04	1.17E-02	*DLEC1:ACAA1:MYD88:OXSR1:SLC22A13*	NA
GWAS catalog	Visceral adipose tissue/subcutaneous adipose tissue ratio	56	5	1.19E-04	1.20E-02	*DNAH10:ZNF664:LARGE:CNTNAP2:RORB*	NA
GWAS catalog	Anxiety and stress-related disorders	15	3	2.64E-04	2.53E-02	*PDE4B:GIGYF2:KCNJ13*	NA
GWAS catalog	Post bronchodilator FEV1 in COPD	38	4	3.12E-04	2.83E-02	*HYKK:CHRNA5:RBMS3:ASAP1*	NA
Chemical_and_Genetic_perturbation	FARMER_BREAST_CANCER_CLUSTER_5	19	5	4.70E-07	1.55E-03	*SUPT4H1:RNF43:MTMR4:RAD51C:TRIM37*	http://www.gsea-msigdb.org/gsea/msigdb/cards/FARMER_BREAST_CANCER_CLUSTER_5
Chemical_and_Genetic_perturbation	BLALOCK_ALZHEIMERS_DISEASE_DN	1236	26	2.06E-05	3.41E-02	*PSMB2:ELAVL4:PDE4B:NMNAT2:SERGEF:COX8A:CCDC92:UGGT2:TM6SF1:HDGFRP3:SUPT4H1:MTMR4:RAD51C:TRIM37:DYNC1I2:SLC25A12:LARGE:PCCB:SNCA:PDE4D:BAI3:PCLO:ORC5:CNTNAP2:DNAJA1:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/BLALOCK_ALZHEIMERS_DISEASE_DN

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
GO_cc	GO_CYTOSKELETAL_PART	1623	31	2.01E-05	2.01E-02	*AGBL4:PDE4B:CEP170:SDCCAG8:ZNF365:KRTAP5-1:KRTAP5-2:KRTAP5-3:KIF18A:MARK2:DNAH10:CCDC92:FAM101A:MYO16:CCNB2:MYO1E:DNAJA3:FAM92B:YWHAE:MYO1C:GABARAP:MYO18A:SEPT4:SKA2:CTDP1:DYNC1I2:OLA1:STAG1:PDE4D:EPB41L2:ASAP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GO_CYTOSKELETAL_PART
Positional_gene_sets	chr17q22	47	10	6.72E-12	2.01E-09	*SUPT4H1:RNF43:HSF5:MTMR4:SEPT4:TEX14:RAD51C:PPM1E:TRIM37:SKA2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr17q22
Positional_gene_sets	chr15q25	73	9	1.27E-08	1.90E-06	*HYKK:PSMA4:CHRNA5:HOMER2:FAM103A1:BTBD1:TM6SF1:HDGFRP3:BNC1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr15q25
Positional_gene_sets	chr17p13	234	12	9.07E-07	9.03E-05	*YWHAE:CRK:MYO1C:DLG4:ACADVL:DVL2:PHF23:GABARAP:CTDNEP1:ELP5:CLDN7:SLC2A4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr17p13
Positional_gene_sets	chr3q22	55	6	7.62E-06	5.69E-04	*PPP2R3A:MSL2:PCCB:STAG1:SLC35G2:NCK1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr3q22
Positional_gene_sets	chr3p22	80	5	6.37E-04	3.55E-02	*DLEC1:ACAA1:MYD88:OXSR1:SLC22A13*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr3p22
Positional_gene_sets	chr2q31	82	5	7.13E-04	3.55E-02	*DYNC1I2:SLC25A12:HAT1:METAP1D:OLA1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr2q31
Positional_gene_sets	chr6q23	49	4	8.31E-04	3.55E-02	*SAMD3:TMEM200A:SMLR1:EPB41L2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/chr6q23
Curated_gene_sets	FARMER_BREAST_CANCER_CLUSTER_5	19	5	4.70E-07	2.59E-03	*SUPT4H1:RNF43:MTMR4:RAD51C:TRIM37*	http://www.gsea-msigdb.org/gsea/msigdb/cards/FARMER_BREAST_CANCER_CLUSTER_5

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
microRNA_targets	ATACTGT_MIR144	199	8	3.36E-04	2.34E-02	*CPEB3:SEMA6D:RNF111:MYO1E:HAT1:STAG1:PDE4D:SNAP91*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATACTGT_MIR144
microRNA_targets	GTTTGTT_MIR495	255	9	3.76E-04	2.34E-02	*CPEB3:SEMA6D:CDH13:GSE1:NUFIP2:LARGE:PDE4D:BAI3:RORB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GTTTGTT_MIR495
microRNA_targets	ATGCTGG_MIR338	112	6	4.20E-04	2.34E-02	*CPEB3:SEMA6D:HMOX2:NUFIP2:SEPT4:MSL2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATGCTGG_MIR338
microRNA_targets	ATGCTGC_MIR103_MIR107	219	8	6.34E-04	2.34E-02	*AGO4:PDE4B:FAM171A1:CPEB3:HDGFRP3:DLG4:MTMR4:RAD51C*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATGCTGC_MIR103_MIR107
microRNA_targets	CACTGTG_MIR128A_MIR128B	337	10	6.99E-04	2.34E-02	*RERE:CCDC92:SEMA6D:CDIP1:DVL2:MTMR4:PPM1E:FAM184A:ORC5:RORB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CACTGTG_MIR128A_MIR128B
microRNA_targets	CACTGCC_MIR34A_MIR34C_MIR449	279	9	7.18E-04	2.34E-02	*AGO4:CPEB3:MARCH5:SLCO3A1:FOXP1:PPP2R3A:MSL2:CNTNAP2:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CACTGCC_MIR34A_MIR34C_MIR449
microRNA_targets	ACTGTGA_MIR27A_MIR27B	473	12	8.34E-04	2.34E-02	*CPEB3:CCDC92:PCDH17:SEMA6D:RNF111:CDIP1:DVL2:MTMR4:PPM1E:STAG1:FAM184A:ORC5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ACTGTGA_MIR27A_MIR27B
microRNA_targets	AGGCACT_MIR5153P	88	5	9.82E-04	2.34E-02	*PCDH17:SEMA6D:SLCO3A1:RNF43:MTMR4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AGGCACT_MIR5153P
microRNA_targets	AATGTGA_MIR23A_MIR23B	418	11	1.02E-03	2.34E-02	*PDE4B:BTAF1:OTUB1:SLC7A1:SEMA6D:HYKK:CRK:NUFIP2:RNF43:ROBO2:MSL2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AATGTGA_MIR23A_MIR23B
microRNA_targets	CCTGCTG_MIR214	237	8	1.06E-03	2.34E-02	*MARK2:PCDH17:UGGT2:BTBD1:MYO18A:NUFIP2:SEPT4:CD47*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CCTGCTG_MIR214

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microRNA_targets	GACAATC_MIR219	142	6	1.45E-03	2.88E-02	*CPEB3:PCDH17:HOMER2:GSE1:PDE4D:RORB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GACAATC_MIR219
microRNA_targets	GAGCCAG_MIR149	144	6	1.56E-03	2.88E-02	*NCDN:B3GAT1:SLCO3A1:DLG4:OXSR1:CD47*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GAGCCAG_MIR149
microRNA_targets	ATAGGAA_MIR202	102	5	1.90E-03	3.14E-02	*CPEB3:ROBO2:MSL2:SNAP91:ASAP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ATAGGAA_MIR202
microRNA_targets	CCCAGAG_MIR326	151	6	1.99E-03	3.14E-02	*METTL15:SEMA6D:KIAA0513:PPM1E:TCF4:OXSR1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CCCAGAG_MIR326
microRNA_targets	ACCATTT_MIR522	162	6	2.82E-03	4.16E-02	*NMNAT2:PRKG1:PPM1E:FOXP1:MSL2:STAG1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/ACCATTT_MIR522
microRNA_targets	TATTATA_MIR374	284	8	3.27E-03	4.43E-02	*PDE4B:DUSP8:ARHGAP28:CNTN4:FOXP1:CD47:PDE4D:RORB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TATTATA_MIR374
microRNA_targets	TTTTGAG_MIR373	225	7	3.41E-03	4.43E-02	*NMNAT2:NAA40:GSE1:DLG4:NUFIP2:MTMR4:PPM1E*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TTTTGAG_MIR373
TF_targets	GFI1_01	263	13	4.77E-07	2.91E-04	*ELAVL4:CPEB3:MARCH5:CDH13:YWHAE:MYO1C:GABARAP:NUFIP2:MTMR4:TCF4:NGEF:PDE4D:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GFI1_01
TF_targets	CAGCTG_AP4_Q5	1501	32	1.45E-06	4.43E-04	*NCDN:CPEB3:MARCH5:MARK2:RCOR2:MACROD1:SPPL3:PCNX:SEMA6D:RNF111:RBFOX1:CDH13:FAM92B:MYO1C:PHF23:MYO18A:MTMR4:SEPT4:PPM1E:SKA2:TCF4:HRC:GIGYF2:KCNJ13:CNTN4:RBMS3:FOXP1:CD47:PPP2R3A:BAI3:DNAJA1:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CAGCTG_AP4_Q5

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
TF_targets	AACTTT_UNKNOWN	1910	36	4.98E-06	8.74E-04	*NCDN:ELAVL4:PDE4B:SERGEF:RCOR2:OTUB1:SEMA6D:CCNB2:MYO1E:SLCO3A1:RBFOX1:CDH13:GABARAP:SLC2A4:MYO18A:PPM1E:TCF4:HAT1:OLA1:GIGYF2:KCNJ13:LARGE:CNTN4:RBMS3:PPP2R3A:STAG1:SNCA:PDE4D:EFNA5:SLIT3:BAI3:PRSS35:FUT9:CNTNAP2:DNAJA1:RORB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AACTTT_UNKNOWN
TF_targets	NKX22_01	189	10	5.73E-06	8.74E-04	*CCDC92:PCDH17:GSE1:CRK:PPM1E:GIGYF2:KCNJ13:FOXP1:SLIT3:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/NKX22_01
TF_targets	TGTTTGY_HNF3_Q6	738	19	2.07E-05	2.53E-03	*RERE:NCDN:ELAVL4:NMNAT2:CPEB3:MARCH5:DUSP8:HOMER2:RBFOX1:TRIM37:TCF4:KCNJ13:FOXP1:PPP2R3A:PDE4D:EFNA5:SLIT3:PRSS35:CNTNAP2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGTTTGY_HNF3_Q6
TF_targets	HAND1E47_01	280	11	3.22E-05	3.27E-03	*NCDN:ELAVL4:RCOR2:SUPT4H1:SEPT4:SLC25A12:NGEF:RBMS3:STAG1:SNCA:SLIT3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HAND1E47_01
TF_targets	TCCATTKW_UNKNOWN	237	10	4.07E-05	3.42E-03	*ELAVL4:OTUB1:CCDC92:ZNF664:RNF111:MYO1E:RBFOX1:MYO18A:RNF43:SEPT4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TCCATTKW_UNKNOWN
TF_targets	RNGTGGGC_UNKNOWN	781	19	4.48E-05	3.42E-03	*RERE:NCDN:ELAVL4:RCOR2:MACROD1:SLCO3A1:GSE1:DVL2:NUFIP2:RNF43:SEPT4:PPM1E:PPFIA3:GIGYF2:RBMS3:FOXP1:MSL2:EFNA5:SLIT3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/RNGTGGGC_UNKNOWN
TF_targets	TAL1BETAE47_01	248	10	5.96E-05	3.82E-03	*ELAVL4:RCOR2:SEMA6D:CTDNEP1:ELP5:TRIM37:GIGYF2:FOXP1:STAG1:RORB*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TAL1BETAE47_01
TF_targets	TAL1ALPHAE47_01	251	10	6.59E-05	3.82E-03	*ELAVL4:PDE4B:RCOR2:SEMA6D:CTDNEP1:ELP5:NUFIP2:TRIM37:FOXP1:STAG1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TAL1ALPHAE47_01
TF_targets	TGGAAA_NFAT_Q4_01	1899	33	6.89E-05	3.82E-03	*RERE:NCDN:ELAVL4:PDE4B:NMNAT2:CPEB3:MARCH5:SLC7A1:HS6ST3:PCNX:SEMA6D:MYO1E:RBFOX1:CRK:MYO1C:GABARAP:NUFIP2:RNF43:*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGGAAA_NFAT_Q4_01

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						SEPT4:TRIM37:SKA2:TCF4:SLC25A12:GIGYF2:KCNJ13:RBMS3:FOXP1:PPP2R3A:STAG1:PDE4D:SLIT3:CNTNAP2:DNAJA1	
TF_targets	CEBP_Q2	234	9	1.99E-04	1.01E-02	*PRKG1:TM6SF1:TCF4:SLC25A12:KCNJ13:FOXP1:STAG1:PDE4D:SLIT3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CEBP_Q2
TF_targets	PTF1BETA_Q6	238	9	2.26E-04	1.06E-02	*PCDH17:CDH13:YWHAE:CRK:DLG4:ACADVL:MTMR4:SYT3:MSL2*	http://www.gsea-msigdb.org/gsea/msigdb/cards/PTF1BETA_Q6
TF_targets	LMO2COM_02	243	9	2.64E-04	1.15E-02	*NCDN:ELAVL4:NMNAT2:RBFOX1:GSE1:MYO18A:NUFIP2:PPM1E:PPP2R3A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/LMO2COM_02
TF_targets	E47_01	252	9	3.45E-04	1.35E-02	*ELAVL4:SERGEF:NAA40:PCDH17:GSE1:CTDNEP1:ELP5:FOXP1:CD47*	http://www.gsea-msigdb.org/gsea/msigdb/cards/E47_01
TF_targets	E47_02	253	9	3.55E-04	1.35E-02	*NCDN:PDE4B:PCDH17:RBFOX1:GSE1:CTDNEP1:ELP5:MYO18A:SEPT4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/E47_02
TF_targets	TAL1BETAITF2_01	258	9	4.09E-04	1.39E-02	*ELAVL4:RCOR2:SEMA6D:CTDNEP1:ELP5:NUFIP2:TRIM37:FOXP1:STAG1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TAL1BETAITF2_01
TF_targets	HLF_01	258	9	4.09E-04	1.39E-02	*ELAVL4:PRKG1:SEMA6D:RBFOX1:NUFIP2:FOXP1:PDE4D:SLIT3:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HLF_01
TF_targets	OCT1_01	264	9	4.83E-04	1.55E-02	*PRKG1:NUFIP2:TCF4:SLC25A12:KCNJ13:FOXP1:PPP2R3A:STAG1:PDE4D*	http://www.gsea-msigdb.org/gsea/msigdb/cards/OCT1_01
TF_targets	GGAMTNNNNNTCCY_UNKNOWN	118	6	5.54E-04	1.69E-02	*NCDN:CLSPN:SDCCAG8:UGGT2:YWHAE:SYT3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GGAMTNNNNNTCCY_UNKNOWN

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TF_targets	MCAATNNNNNGCG_UNKNOWN	84	5	7.96E-04	2.31E-02	*RERE:PCDH17:TEX14:RAD51C:SLIT3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/MCAATNNNNNGCG_UNKNOWN
TF_targets	GATAAGR_GATA_C	298	9	1.14E-03	3.16E-02	*NCDN:ELAVL4:GSE1:MYO1C:CLDN7:MYO18A:PPM1E:KCNJ13:PPP2R3A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/GATAAGR_GATA_C
TF_targets	LXR_DR4_Q3	92	5	1.20E-03	3.18E-02	*RBFOX1:SLC2A4:SKA2:SYT3:FOXP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/LXR_DR4_Q3
TF_targets	TGCCAAR_NF1_Q6	715	15	1.34E-03	3.28E-02	*SDCCAG8:MARK2:RCOR2:BNC1:RBFOX1:CRK:CTDNEP1:ELP5:TCF4:HRC:SLC35G2:SLIT3:PRSS35:APTX:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGCCAAR_NF1_Q6
TF_targets	HMGIY_Q6	246	8	1.34E-03	3.28E-02	*SLC7A1:TM6SF1:RNF43:SKA2:CNTN4:FOXP1:PPP2R3A:PDE4D*	http://www.gsea-msigdb.org/gsea/msigdb/cards/HMGIY_Q6
TF_targets	AR_03	58	4	1.57E-03	3.68E-02	*RERE:NCDN:ELAVL4:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AR_03
TF_targets	SF1_Q6	257	8	1.77E-03	3.95E-02	*NCDN:NAA40:OTUB1:MACROD1:CCDC92:ZNF664:SLC2A4:PPM1E*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SF1_Q6
TF_targets	SRY_02	258	8	1.81E-03	3.95E-02	*ELAVL4:CCDC92:ZNF664:SLC7A1:RBFOX1:MYO18A:RNF43:TCF4*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SRY_02
TF_targets	BACH1_01	262	8	1.99E-03	4.03E-02	*NCDN:PCDH17:GSE1:DLG4:ACADVL:PHF23:GIGYF2:FAM184A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/BACH1_01
TF_targets	PAX4_01	263	8	2.04E-03	4.03E-02	*NCDN:GSE1:PHF23:NUFIP2:GIGYF2:RBMS3:PDE4D:EFNA5*	http://www.gsea-msigdb.org/gsea/msigdb/cards/PAX4_01

Category	Gene-Set	Number of Genes in Set	Number of Overlapping Genes	P-value	Adjusted P-value	Genes	Link
TF_targets	YGCGYRCGC_UNKNOWN	325	9	2.07E-03	4.03E-02	*RBFOX1:GSE1:YWHAE:PPM1E:SLC25A12:METAP1D:MSL2:IMMP2L:DNAJA1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/YGCGYRCGC_UNKNOWN
TF_targets	AP4_Q5	266	8	2.19E-03	4.03E-02	*NCDN:CPEB3:SEMA6D:MYO1C:PHF23:RBMS3:DNAJA1:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AP4_Q5
TF_targets	RP58_01	208	7	2.20E-03	4.03E-02	*RCOR2:SEMA6D:RBFOX1:TRIM37:GIGYF2:FOXP1:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/RP58_01
TF_targets	AP1_Q2_01	270	8	2.40E-03	4.03E-02	*NCDN:ELAVL4:HOMER2:GSE1:DLG4:ACADVL:TCF4:BRINP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/AP1_Q2_01
TF_targets	CACCCBINDINGFACTOR_Q6	270	8	2.40E-03	4.03E-02	*RCOR2:OTUB1:PCDH17:GSE1:YWHAE:CRK:MYO1C:RBMS3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CACCCBINDINGFACTOR_Q6
TF_targets	SRF_C	212	7	2.45E-03	4.03E-02	*ELAVL4:SLC7A1:MYO1E:CRK:SLC2A4:FOXP1:PPP2R3A*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SRF_C
TF_targets	CEBP_01	271	8	2.46E-03	4.03E-02	*NCDN:RBFOX1:CDH13:SUPT4H1:RNF43:PPM1E:GIGYF2:FOXP1*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CEBP_01
TF_targets	CTGCAGY_UNKNOWN	763	15	2.51E-03	4.03E-02	*NCDN:ELAVL4:DUSP8:RCOR2:PCDH17:CDH13:YWHAE:MYO18A:SEPT4:SYT3:RBMS3:FOXP1:STAG1:PDE4D:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/CTGCAGY_UNKNOWN
TF_targets	SMTTTTGT_UNKNOWN	405	10	2.74E-03	4.28E-02	*ELAVL4:NMNAT2:SLC7A1:RBFOX1:GSE1:YWHAE:RNF43:TCF4:FOXP1:PDE4D*	http://www.gsea-msigdb.org/gsea/msigdb/cards/SMTTTTGT_UNKNOWN
TF_targets	TGCGCANK_UNKNOWN	554	12	3.13E-03	4.77E-02	*ELAVL4:SDCCAG8:PSMA4:RBFOX1:YWHAE:CRK:DVL2:SLC2A4:CD47:MSL2:PDE4D:BAI3*	http://www.gsea-msigdb.org/gsea/msigdb/cards/TGCGCANK_UNKNOWN

Supplementary Table 5. 12: Polygenic Scores for Each Latent Cognitive Factor Predicting Schizophrenia and Schizophrenia Symptom Dimensions in Individuals from the TOP Study

Cognitive Factor 1				
Target Phenotype	**Beta**	**SE**	**R^2**	**P**
Schizophrenia	-0.33	0.07	2.59E-02	**2.48E-06**
Positive Symptoms	0.27	0.32	2.56E-03	3.97E-01
Negative Symptoms	-0.04	0.38	4.85E-05	9.07E-01
General Psychopathology	-0.13	0.26	8.46E-04	6.25E-01

Cognitive Factor 2				
Target Phenotype	**Beta**	**SE**	**R^2**	**P**
Schizophrenia	-0.21	0.07	1.11E-02	**1.80E-03**
Positive Symptoms	-0.32	0.32	3.72E-03	3.06E-01
Negative Symptoms	-0.60	0.38	8.80E-03	1.15E-01
General Psychopathology	-0.18	0.26	1.61E-03	5.00E-01

Cognitive Factor 3				
Target Phenotype	**Beta**	**SE**	**R^2**	**P**
Schizophrenia	-0.11	0.07	3.03E-03	1.02E-01
Positive Symptoms	-0.38	0.32	4.81E-03	2.45E-01
Negative Symptoms	-0.54	0.38	6.97E-03	1.61E-01
General Psychopathology	-0.26	0.27	3.36E-03	3.30E-01