An integrative analysis of genetics, brain structure, and childhood trauma in antipsychotic treatment response: toward a unified view of treatment outcome in schizophrenia

by

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ABSTRACT

Schizophrenia is a debilitating neuropsychiatric disorder affecting approximately 1% of the global population. Unfortunately, antipsychotic treatment is ineffective in 50% of patients. The complex, heterogeneous and multifactorial nature of antipsychotic response presents a challenge with respect to elucidating the underlying mechanisms. Although genetic, neuroimaging, and clinical studies of antipsychotic response have shown much progress and potential, clinically actionable findings remain incredibly limited. This has hindered the progress toward more personalised treatment approaches, highlighting the necessity of implementing larger cohorts and more integrated approaches in antipsychotic treatment response studies. Genetic and brain structural variation has been widely implicated in antipsychotic response, and there is emerging evidence for a role of childhood trauma in differential treatment outcomes. Although imaging genetics and gene-environment interaction (GxE) studies have begun to disentangle the underlying relationships between these variables, studies of this nature in antipsychotic response remain scarce.

This study aimed to investigate the interplay between genetics, brain structure, childhood trauma, and antipsychotic response, using an integrative approach. This was done with a cohort of 103 first-episode schizophrenia patients treated with a long-acting injectable antipsychotic. Data was available for genome-wide variants, baseline regional brain volumes, childhood trauma severity, and treatment response. Candidate genes previously associated with both brain structure and antipsychotic response were selected from literature. From the available genotype data, variants within these genes were extracted and prioritised using a bioinformatics pipeline. Next, based on previous associations with antipsychotic response in literature, brain regions of interest (ROIs) were identified in the available neuroimaging data. Linear regression was used to conduct association analyses exploring the roles of ROIs in treatment response, childhood trauma in antipsychotic response/brain structure, imaging genetics in antipsychotic response, and imaging gene-environment interactions in antipsychotic response.

Ten genetic variants in *CACNA1C*, *NRG1*, and *OXTR* were significantly associated with antipsychotic response, after correction for multiple testing; $\alpha=6.720\times10^{-5}$ (additive model), $\alpha=9.470\times10^{-5}$ (genotypic model). Thirty-four significant associations with antipsychotic response were identified for GxE with childhood trauma and variants in *CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR*; $\alpha=1.120\times10^{-5}$ (additive model), $\alpha=1.578\times10^{-5}$ (genotypic model). None of the remaining association analyses yielded significant results, so an unadjusted threshold ($\alpha=0.05$) was considered for the exploratory observation of imaging genetic and imaging gene-environment interaction trends of interest. Five GxE significantly associated with improved response to antipsychotics showed tentative trends for increased putamen and hippocampal volumes. Conversely, six GxE significantly associated with poorer treatment response showed trends for reduced volumes of the caudate, cortex, pallidum, putamen, subcortical grey matter, and total grey matter. These findings highlighted a trend-level positive correlation between baseline ROI volumes and treatment response (i.e. larger ROI volumes and improved antipsychotic response, and vice versa).

The tentative positive correlation between ROI volumes and antipsychotic response in the context of GxE suggests a mechanism through which the relationship between brain structure and antipsychotic response may be mediated. Overall, the novel significant associations, and trends of interest, provide support for the utility of integrated research approaches to more effectively disentangle relationships between underlying molecular mechanisms and heterogeneous treatment response phenotypes.

OPSOMMING

Skisofrenie is 'n verswakkende neuropsigiatriese versteuring wat ongeveer 1% van die wêreldbevolking aantas. Ongelukkig is antipsigotiese behandeling oneffektief in ongeveer 50% van pasiënte. Die komplekse, heterogene en multifaktoriale aard van antipsigotiese reaksie bied 'n uitdaging met betrekking tot die toeligting van die onderliggende meganismes. Alhoewel genetiese, brein beelding en kliniese studies van antipsigotiese reaksie baie vooruitgang en potensiaal getoon het, bly kliniese werkbare bevindings ongelooflik beperk. Dit het die vordering na meer verpersoonlikte behandelingsbenaderings belemmer, en dit het die noodsaaklikheid van die implementering van groter kohorte en meer geïntegreerde benaderings in antipsigotiese behandelingsresponse uitgelig. Genetiese en breinstruktuurvariasie is bekend om betrokke te wees by antipsigotiese reaksie, en daar is opkomende bewyse vir die rol van kindertyd trauma in die differensiële uitkoms van behandeling. Alhoewel die beeldings genetika en gene-omgewing interaksie (GxE) studies begin het om die onderliggende verwantskappe tussen hierdie veranderlikes te ontrafel, bly studies van hierdie aard in antipsigotiese reaksie skaars.

Hierdie studie mik om die wisselwerking tussen genetika, breinstruktuur, kindertyd trauma en antipsigotiese respons met behulp van 'n geïntegreerde benadering te ondersoek. 'n Groep van 103 pasiënte met die eerste episode van skisofrenie wat behandel is met 'n langwerkende inspuitbare antipsigotiese middle is gebruik vir hierdie studie. Data was beskikbaar vir genoomwye variante, basislyn streeksbreinvolumes, erns van kindertyd trauma en die respons van behandeling. Kandidaatgene wat voorheen met beide breinstruktuur en antipsigotiese respons geassosieer is, is uit die literatuur gekies. Uit die beskikbare genotipe-data is variante binne hierdie gene onttrek en geprioritiseer met behulp van 'n bioinformatika-pyplyn. Volgende, op grond van vorige assosiasies met antipsigotiese respons in die literatuur, is breinstreke van belang (ROIs) geïdentifiseer in die beskikbare brein beeld data. Lineêre regressie is gebruik om assosiasieanalises te doen om die rolle van ROIs in behandelingsrespons, kindertyd trauma in antipsigotiese reaksies/breinstruktuur te ondersoek, genetiese beeldvorming in antipsigotiese reaksies te ondersoek, en geen-omgewing interaksies in antipsigotiese respons te beeld.

Tien genetiese variante in *CACNA1C*, *NRG1* en *OXTR* het betekenisvolle assosiasie met antipsigotiese respons, na regstelling vir veelvoudige toetsing; $\alpha=6.720\times10^{-5}$ (toevoegingsmodel), $\alpha=9.470\times10^{-5}$ (genotipiese model). Vier-en-dertig betekenisvolle assosiasies met antipsigotiese respons is geïdentifiseer vir GxE met kindertyd trauma en variëteite in *CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1* en *OXTR*; $\alpha=1.120\times10^{-5}$ (aanvullende model), $\alpha=1.578\times10^{-5}$ (genotipiese model). Nie een van die oorblywende assosiasie-ontledings het beduidende resultate opgelewer nie, en 'n onaangepaste drempel ($\alpha=0,05$) is oorweeg vir die ondersoekende waarneming van genetiese beeldvorming en interaksie-neigings in gene-omgewing interaksie. Vyf GxE wat aansienlik geassosieer is met 'n verbeterde reaksie op antipsigotiese middels, toon tentatiewe neigings vir verhoogde putamen en hippocampus volumes. Aan die ander kant het ses GxE wat aansienlik geassosieer is met 'n swakker behandelingsrespons, neigings getoon vir verminderde volumes van die caudaat, korteks, pallidum, putamen, subkortikale grysstof en totale grysstof. Hierdie bevindings het 'n positiewe korrelasie op tendensvlak uitgelig tussen basislyn ROI volumes en behandelingsrespons (d.w.s. groter ROI volumes en verbeterde antipsigotiese respons, en omgekeerd).

Die tentatiewe positiewe korrelasie tussen ROI volumes en antipsigotiese respons in die konteks van GxE dui op 'n meganisme waardeur die verhouding tussen breinstruktuur en antipsigotiese respons bemiddel kan word. In die geheel bied die nuwe betekenisvolle assosiasies, en tendense van belang, die nut van geïntegreerde navorsingsbenaderings om die verhoudings tussen onderliggende molekulêre meganismes en heterogene behandelingsrespons fenotipes meer effektief te ontkoppel.

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LIST OF SYMBOLS AND ABBREVIATIONS

3’	3-prime end
α	Alpha
&	And
~	Approximately
=	Equal to
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
x	Multiplied by / Interaction
%	Percentage
±	Standard deviation
A	Adenine
ACC	Anterior cingulate cortex
ACE	Adverse Childhood Experiences
ADRs	Adverse drug reactions
AIMs	Ancestry informative markers
AKT1	Akt serine/threonine kinase 1 gene
Alt	Alternate allele
Anc	Ancestral allele
ANK3	Ankyrin 3 gene
ANKS1B	Ankyrin repeat and sterile alpha motif domain containing 1B gene
AP	Antipsychotic
ASL	Arterial spin labelling
ATR	Antipsychotic treatment response
BDNF	Brain derived neurotrophic factor gene
bp	Base pairs
BPRS	Brief Psychiatric Rating Scale
C	Cytosine
CACNA1C	Calcium voltage-gated channel subunit alpha-1C gene
cAMP	Cyclic adenosine monophosphate
CGI	Clinical Global Impressions Scale
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
Chr	Chromosome
CI	Confidence interval
CLES	Children’s Life Events Scale
CNR1	Cannabinoid receptor 1 gene
CNV	Copy number variation
COMT	Catechol-O-methyltransferase gene
CSAS	Childhood Sexual Assaults Scale
CT	Computed tomography
CTQ	Childhood Trauma Questionnaire
CYP	Cytochrome P450 enzyme
CYP	Cytochrome P450 gene
CYP1A2	Cytochrome P450, family 1, subfamily A, polypeptide 2 enzyme
CYP2A4	Cytochrome P450, family 2, subfamily A, polypeptide 4 enzyme
CYP2C9	Cytochrome P450, family 2, subfamily C, polypeptide 9 gene
CYP2C19	Cytochrome P450, family 2, subfamily C, polypeptide 19 enzyme
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6 enzyme
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6 gene
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4 gene
CYP3A5	Cytochrome P450, family 3, subfamily A, polypeptide 5 gene
D’	Normalised measure of allelic association
D_2	Dopamine type 2
DISC1	Disrupted in schizophrenia 1 gene
DNA	Deoxyribonucleic acid

DRD2	Dopamine receptor D2 gene
DRD3	Dopamine receptor D3 gene
DRD4	Dopamine receptor D4 gene
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion tensor imaging
DTNBP1	Dystrobrevin binding protein 1 gene
DUP	Duration of untreated psychosis
EHF	E26 transformation-specific homologous factor
ENIGMA	Enhancing Neuroimaging Genetics through Meta-analysis
EPS	Extrapyramidal side effects
eQTL	Expression quantitative trait loci
ErbB4	Erb-B2 Receptor Tyrosine Kinase 4
ESRS	Extrapyramidal Symptom Rating Scale
et al.	*Et alii*
ETI-SR	Early Trauma Inventory Self Report
FES	First-episode schizophrenia
FGAs	First generation antipsychotics
fMRI	Functional magnetic resonance imaging
G	Guanine
GxE	Gene-environment interactions
GABA	Gamma aminobutyric acid
gDNA	Genomic DNA
GRCh37	Genome Reference Consortium human genome build 37
GRCh38	Genome Reference Consortium human genome build 38
GRM3	Glutamate metabotropic receptor 3 gene
GWAS	Genome-wide association studies
Hg38	Human genome build 38
HPA	Hypothalamic-pituitary-adrenal axis
HREC	Human Research and Ethics Committee
HTR1A	5-hydroxytryptamine (serotonin) receptor 1A gene
HTR2A	5-hydroxytryptamine (serotonin) receptor 1A gene
HWE	Hardy-Weinberg equilibrium
ICA	Independent component analysis
ID	Identification/ identifier
i.e.	*Id est*
iGxE	Imaging gene-environment interactions
IL1RN	Interleukin receptor 1 antagonist gene
iPOP	Integrative personal omics profile
iPSC	Induced pluripotent stem cell
KEGG	Kyoto Encyclopedia of Genes and Genomes
LAI	Long-acting injectable
LD	Linkage disequilibrium
LTD	Long-term depression
LTP	Long-term potentiation
MAF	Minor allele frequency
MAPK	Mitogen-activated protein kinase
Met	Methionine
mg	Milligrams
miRNA	MicroRNA
mm	Millimetres
mm^3	Millimetres cubed
MMP9	Matrix metallopeptidase 9 gene
MRI	Structural magnetic resonance imaging
ms	Milliseconds

MTG	Middle temporal gyrus
N	Number of samples
n	Number of tests
NA	Not applicable
NCAN	Neurocan gene
ND	Not determined
NHGRI-EBI	National Human Genome Research Institute – European Bioinformatics Institute
NMD	Nonsense-mediated mRNA decay
NRF	National Research Foundation
NRG1	Neuregulin 1 gene
NRGN	Neurogranin gene
OXT	Oxytocin I prepropeptide gene
OXTR	Oxytocin receptor gene
P	Probability
PANSS	Positive and Negative Syndrome Scale
PET	Positron emission tomography
PGC	Psychiatric Genomics Consortium
PharmGKB	Pharmacogenomics Knowledge Base
PRS	Polygenic risk scores
PolymiRTS	Polymorphisms in miRNA and their target sites
PolyPhen-2	Polymorphism Phenotyping version 2
PSQ	Personal Safety Questionnaire
QC	Quality control
Q-Q	Quantile-quantile
r^2	Squared correlation co-efficient
rGE	Gene-environment correlations
RGS4	Regulation of G protein signalling 4 gene
RNA	Ribonucleic acid
ROIs	Regions of interest
rSNPs	Regulatory SNPs
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-IV
SES	Socioeconomic status
SGAs	Second generation antipsychotics
SIFT	Sorting Intolerant from Tolerant
SNPs	Single nucleotide polymorphisms
SPECT	Single photon emission computed tomography
T	Thymine
TCF4	Transcription factor 4 gene
TF	Transcription factor
TFBS	Transcription factor binding site
TLEQ	Traumatic Life Events Questionnaire
TNFα	Tumor necrosis factor gene
USA	United States of America
UTR	Untranslated region
v	Version
Val	Valine
vs.	Versus
WGES	Whole genome/ exome sequencing studies
ZNF804A	Zinc finger protein 804A gene

CHAPTER 1

Literature review

1.1. Schizophrenia

1.1.1. Symptoms and diagnosis

Schizophrenia is a chronic and debilitating neuropsychiatric disorder affecting more than 21 million individuals globally (Charlson et al., 2018). The majority of affected individuals reside in low- and middle-income countries, yet these countries represent the highest proportions of untreated individuals (Demyttenaere et al., 2004), with only 31% of affected individuals having access to treatment (Lora et al., 2012). Schizophrenia is a leading contributor to the global disease burden and was reported to be the 12th most disabling disorder among 310 diseases and injuries according to the Global Burden of Disease study in 2016 (Charlson et al., 2018). In addition to the severe negative impact on patients' quality of life, schizophrenia poses a tremendous socioeconomic burden (Chong et al., 2016).

Schizophrenia is complex and pervasive, manifesting as a broad range of symptoms (Owen et al., 2016). The diverse psychopathology of the disorder includes core features which are categorised as positive or psychotic symptoms (i.e. delusions and hallucinations), negative symptoms (i.e. speech impairments and emotional withdrawal), and general or cognitive symptoms (i.e. mood and cognitive impairments; Owen et al., 2016). Several clinical measurement tools have been developed to quantify these symptoms, including the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), the Scales for the Assessment of Negative and Positive Symptoms (SANS and SAPS; Andreasen, 1983; 1984), and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). The most common of these is the PANSS, which is a 30-item rating scale divided into positive (seven items), negative (seven items) and general symptom domains (16 items), as shown in Table 1.1. Each of these items is scored according to severity from 1 (absent) to 7 (extreme), conferring a baseline score of 30, and a maximum possible score of 210. Aside from measuring symptom severity, the PANSS is widely used to monitor response to treatment (Levine et al., 2011).

Table 1.1. The symptoms of schizophrenia as measured by the PANSS (Kay et al., 1987).

Positive symptoms	Negative symptoms	General symptoms
Conceptual disorganisation	Blunted affect	Active social avoidance
Delusions	Difficulty in abstract thinking	Anxiety
Excitement	Emotional withdrawal	Depression
Grandiosity	Lack of spontaneity	Disorientation
Hallucinatory behaviour	Poor rapport	Disturbance of volition
Hostility	Social withdrawal	Guilt feelings
Suspiciousness	Stereotyped thinking	Lack of judgment and insight
		Mannerisms and posturing
		Motor retardation
		Poor attention
		Poor impulse control
		Preoccupation
		Somatic concern
		Tension
		Uncooperativeness
		Unusual thought content

The diagnosis of schizophrenia involves the assessment of patient-specific signs and symptoms as described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013). Here, it is proposed that for an individual to be diagnosed with schizophrenia, two or more of the following active-phase symptoms need to be present for a minimum of one month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, and negative symptoms (American Psychiatric Association, 2013). Furthermore, at least one of these qualifying symptoms must be delusions, hallucinations, or disorganized speech (American Psychiatric Association, 2013). In addition to this a decreased level of functioning with regard to work, interpersonal relationships, or self-care, should be evident (American Psychiatric Association, 2013). Due to the heterogeneity in disorder manifestation, and the symptomatic overlap observed among schizophrenia and other psychiatric disorders (Figure 1.1), a comprehensive assessment of individuals is necessary to make a definitive diagnosis (Patel et al., 2014). This includes careful evaluation of illness duration, the timing of delusions or hallucinations, and severity of manic or depressive symptoms (Patel et al., 2014).

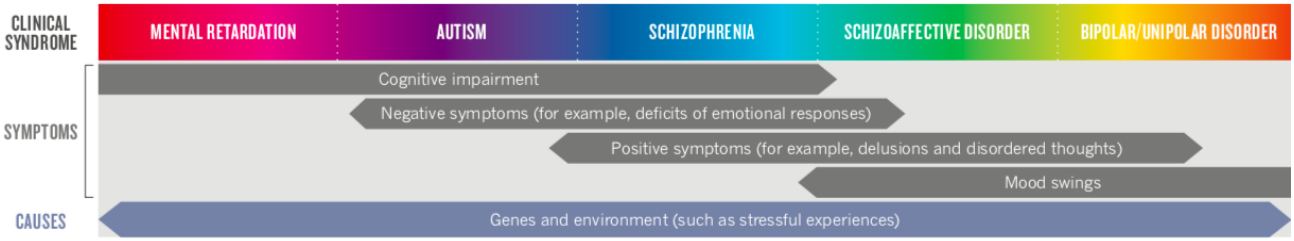


Figure 1.1. A depiction of the overlapping symptoms in psychiatric disorders (Adam, 2013). *Reproduced with permission from Springer Nature*.

1.1.2. Pathophysiology

Despite numerous clinical, pharmacological, physiological and brain imaging studies, there is a limited understanding of the underlying mechanisms contributing to schizophrenia pathophysiology. That said, there is a growing body of evidence suggesting that dysfunctional neurotransmission plays a role in schizophrenia, including either an excess or deficiency of dopamine, serotonin, and glutamate neurotransmitters (Patel et al., 2014). Specifically, there is strong evidence implicating dysfunctional dopaminergic neurotransmission in the manifestation of positive symptoms (Owen et al., 2016; Patel et al., 2014). Furthermore, it has been suggested that abnormal glutamate signalling may contribute to the underlying pathophysiology of negative and cognitive symptoms (Owen et al., 2016; Patel et al., 2014).

A multitude of neuroimaging studies have identified structural and functional brain alterations in individuals with schizophrenia, yet none of these abnormalities are exclusively related to this disorder (Linden, 2012). This is not unexpected considering the heterogeneity of schizophrenia psychopathology, and the symptomatic overlap with other psychiatric conditions (Owen et al., 2016). However, the lack of distinctive biological correlates of schizophrenia highlights a clear deficit with respect to the discovery of reliable biomarkers for illness diagnosis (Linden, 2012). Despite these shortcomings, there has been some advancement in terms of relating aspects of schizophrenia to specific underlying neurobiology. For example, many studies have provided evidence for the involvement of the prefrontal cortex in cognitive deficits relating to working memory

and executive control (Barch and Ceaser, 2012; Lewis, 2012; Meyer-Lindenberg and Tost, 2014). Additionally, numerous studies have demonstrated reductions in grey matter, and abnormalities in white matter, in many areas of the brain (Haijma et al., 2013). In addition to the prefrontal cortex, brain regions repeatedly implicated in schizophrenia include, but are not limited to, the hippocampus, anterior cingulate cortex, temporal lobe, caudate nucleus, and thalamus (Haijma et al., 2013; Lieberman et al., 2018; Owen et al., 2016; Tamminga and Medoff, 2002).

1.1.3. Risk factors and genetics

Despite over a century of research, the aetiology of schizophrenia remains incompletely understood. However, it is widely accepted that this disorder may arise from a combination of multiple genetic and environmental influences (Stefansson et al., 2009). Environmental factors that have been implicated in increased risk for psychosis include prenatal exposures such as stress and infection, perinatal hypoxia, malnutrition, experience of traumatic events including childhood maltreatment, male gender, high paternal age, urbanicity, poverty, lower socio-economic class, and cannabis use, among others (Bernardo et al., 2013; Clarke et al., 2012). Aside from environmental contributors, genetic predisposition remains the strongest risk factor, with the most reliable predictor for the development of schizophrenia being a family history of the disorder (Gareeva and Khusnutdinova, 2018).

Considering that schizophrenia is the most heritable of the psychiatric disorders, with approximately 81% heritability, it is not surprising that there is a wealth of studies aimed at better characterising the genetic underpinnings of the disorder (Gareeva and Khusnutdinova, 2018). Despite this, the exact genetic elements continue to elude scientists due to the non-Mendelian nature of schizophrenia. However, extensive research has unveiled numerous important findings that have contributed to our understanding of disorder risk (Gareeva and Khusnutdinova, 2018). These findings have arisen from the earlier linkage studies in families, as well as association studies that made use of candidate gene approaches, followed by the implementation of hypothesis-free genome-wide association studies (GWAS), genome-wide copy number variation (CNV) studies, and whole genome/ exome sequencing studies (WGES; Drögemöller, 2013). These studies have shown that disorder risk can be attributed to numerous common genetic variants each contributing very small effects in a cumulative fashion, and by a small number of highly penetrant variants with larger effects (Henriksen et al., 2017). Overall, the genetic architecture of schizophrenia has proven to be highly complex, heterogeneous, and polygenic (Henriksen et al., 2017). In fact, more recently it has been suggested that an omnigenic model may be more appropriate to explain the underlying mechanisms of the disorder (Boyle et al., 2017). This means that all genes expressed in the relevant tissue (e.g. the brain in schizophrenia) may contribute to disorder risk (Boyle et al., 2017). This may contribute to the so-called “missing heritability” observed, i.e. all significant GWAS hits considered together only account for a modest fraction of the predicted genetic variance (Boyle et al., 2017). To date, over 100 genetic loci have been associated with schizophrenia (Henriksen et al., 2017; Ripke et al., 2014). However, important to note here is that statistical associations do not necessarily imply causal pathways (Henriksen et al., 2017). Furthermore, there is increasing evidence for genetic overlap among numerous psychiatric disorders, so many genetic associations identified are not specific to schizophrenia (Henriksen et al., 2017; O’Connell et al., 2018). Overall, extensive research is still

required to elucidate the aetiology of schizophrenia, and to identify robust biomarkers to enable reliable disorder diagnosis (Henriksen et al., 2017).

1.2. Antipsychotic treatment of schizophrenia

1.2.1. Background

The treatment of schizophrenia was revolutionised in the 1950s with the serendipitous discovery of the antipsychotic drug chlorpromazine (Owen et al., 2016). This led to the development of over 60 different antipsychotics, all of which include blockade of the dopamine D_2 receptor in their mechanism of action (McCutcheon et al., 2019; Tandon, 2011). To this day, antipsychotics remain the only available therapeutic agents for the effective treatment of schizophrenia (McCutcheon et al., 2019; Tandon et al., 2010). These drugs are traditionally divided into two general categories: the earlier, typical or first-generation antipsychotics (FGAs), and atypical or second-generation antipsychotics (SGAs) – the first of which was clozapine that was introduced in the late 1960s (Lally and MacCabe, 2015; Tandon, 2011). Although the precise mechanism of action of antipsychotic drugs has not been fully characterised, SGAs have a wider range of neurochemical targets. In addition to the dopaminergic pathway, these drugs may also involve serotonergic, glutamatergic and alpha-adrenergic systems (Correll, 2010; Meltzer, 2013). FGAs commonly involve high dopamine antagonism and low serotonin antagonism, and SGAs can be divided into those that demonstrate moderate-to-high dopamine antagonism along with high serotonin antagonism, and those that have low dopamine antagonism along with high serotonin antagonism (Patel et al., 2014).

The most distinguishing characteristic between FGAs and SGAs is the differential incidence of adverse drugs reactions (ADRs; Lally and MacCabe, 2015; Meltzer, 2013). Antipsychotics can induce a diverse range of ADRs that are severe, and can be long-lasting (Kaar et al., 2019; Tandon, 2011). Treatment with FGAs is most often accompanied by motor abnormalities (Meltzer, 2013; Tandon et al., 2010). These include extrapyramidal side effects (EPS) which are either reversible (i.e. parkinsonism), or chronic (i.e. tardive dyskinesia; Tandon et al., 2010). On the other hand, SGAs are predominantly associated with weight gain and other metabolic adverse effects, despite the significantly lower risk of developing EPS (Tandon et al., 2010).

The treatment of schizophrenia is complicated, and each patient requires careful monitoring for the most appropriate decisions to be made with regard to the choice and dosage of drugs (Drögemöller, 2013; Pouget et al., 2014). In the case of inadequate response to first line treatment, either the dosage can be increased, or an alternate antipsychotic can be administered (Drögemöller, 2013). Based on consensus recommendations by experts, before altering the treatment, first line treatment should be continued for three to six weeks in the case of little to no response, and for four to 10 weeks if partial response is observed (Buckley, 2008). Antipsychotics are generally successful in the treatment of positive symptoms of schizophrenia, yet are minimally effective for reducing negative and cognitive symptoms. There is no significant evidence for clear differences in the efficacy profiles between FGAs and SGAs (Lally and MacCabe, 2015), with the exception of clozapine, which demonstrates clear superiority in efficacy and response in treatment refractory patients, along with reductions of suicide (Kane et al., 1988; Meltzer et al., 2003; Shah et al., 2019). However, clozapine use

may result in agranulocytosis, a severe and potentially life-threatening ADR, therefore clozapine is not administered in the first line of treatment in most cases (Chowdhury et al., 2011; McCutcheon et al., 2019).

1.2.2. Treatment response

The goal of antipsychotic treatment is to achieve and maintain remission without relapse. Reviews of treatment outcomes in first-episode schizophrenia (FES) patients concluded that up to 22% of patients may achieve remission within the first five years without relapse (Altamura et al., 2007; Carbon and Correll, 2014; Ram et al., 1992). Unfortunately, 80% to 85% of individuals experience relapse after an initial period of favourable response during the first five years of illness (Altamura et al., 2007; Carbon and Correll, 2014; Lang et al., 2013; Robinson et al., 1999). Furthermore, approximately 50% of treated patients are minimally- or non-responsive (treatment refractory; Lohoff and Ferraro, 2010). With the observation of the vast variability in response to antipsychotics between individuals with schizophrenia, it quickly became apparent that treatment response is a highly complex and heterogeneous trait, much like the disorder itself (Drögemöller, 2013).

Treatment regiments have not been standardised, although response is commonly monitored and evaluated using symptom severity scales (Leucht et al., 2008). For instance, overall improvement can be determined by comparing BPRS or PANSS total scores before and after treatment (Emsley et al., 2006; Remington et al., 2010). Earlier studies of treatment response considered a less than 20% improvement in BPRS/ PANSS scores as an indication of non-response (Emsley et al., 2006). Improvement in specific symptom domains can be evaluated by comparing pre- and post-treatment SANS scores, SAPS scores, or PANSS positive, negative, and general scores (Remington et al., 2010). The lack of a standardised definition for antipsychotic treatment outcome has drastically hindered cross-study comparison. In 2005, the Remission in Schizophrenia Working Group recognised this issue and came to a consensus on criteria to define remission across the SAPS, SANS, PANSS, and BPRS (Andreasen et al., 2005). According to these criteria, remission is defined by simultaneous ratings of mild, or less, for a specific set of symptoms, for a period of six months (Andreasen et al., 2005). The proposed symptom items for the PANSS are delusions, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerisms/ posturing, blunted affect, social withdrawal, and lack of spontaneity (Andreasen et al., 2005). Related items were selected across the SAPS, SANS, and BPRS for evaluating overall remission (Andreasen et al., 2005). On the other end of the response spectrum, patients are considered to be treatment refractory if there is a lack of improvement in symptoms after successive treatments with two different antipsychotics for at least six weeks each, with particular reference to positive symptoms (Suzuki et al., 2012). In these cases, clozapine is usually prescribed, as it has proven to be the most effective drug for the treatment of refractory individuals (Chowdhury et al., 2011; Shah et al., 2019). Clozapine use is therefore typically regarded as an indication of treatment resistance (Shah et al., 2019). An overview of concepts (i.e. remission, relapse, and refractoriness) that are central to the consideration of treatment response outcomes is outlined in Figure 1.2 (Drögemöller, 2013).

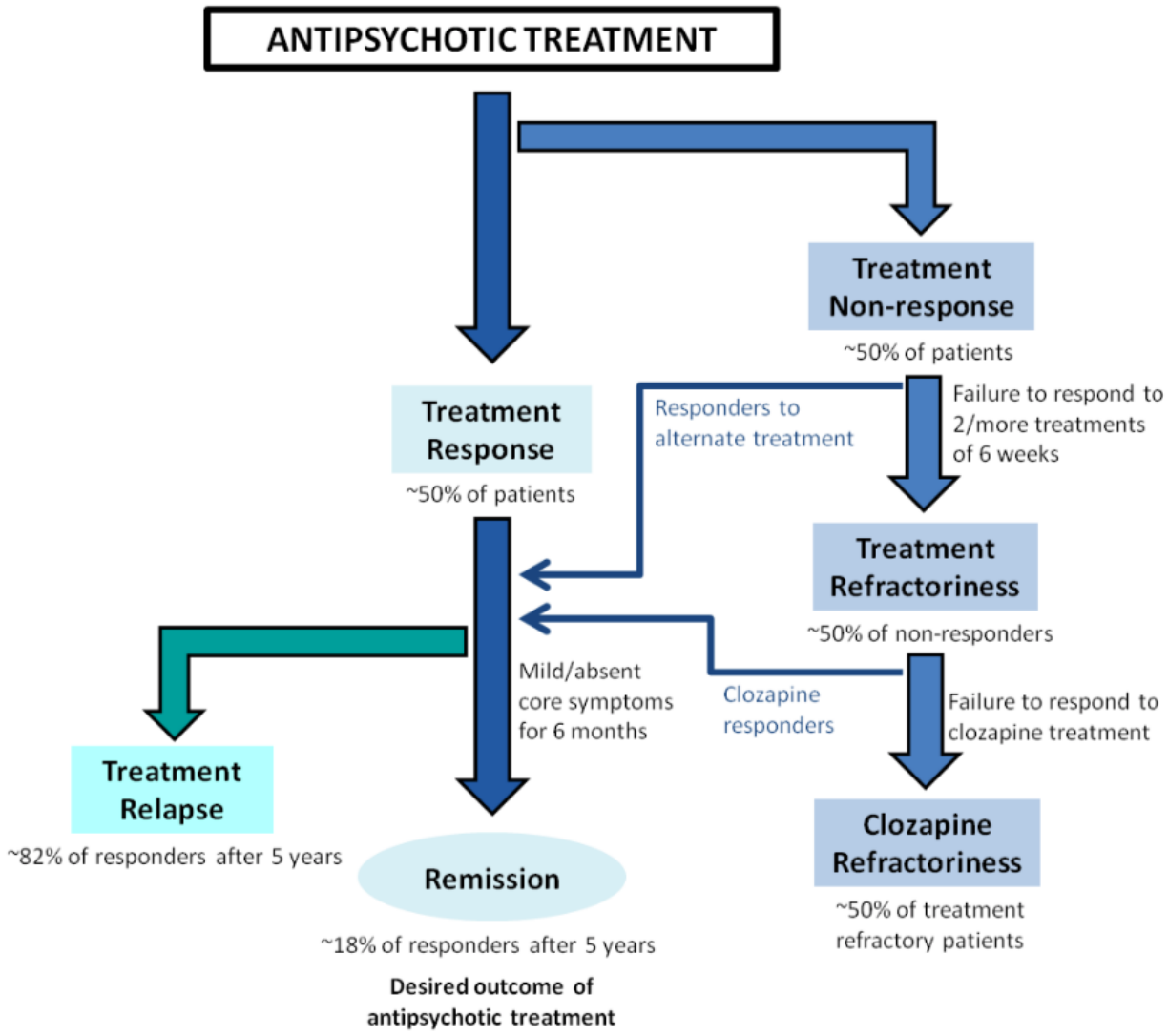


Figure 1.2. An overview of the core features of antipsychotic treatment response (Drögemöller, 2013). *Reproduced from the unpublished doctoral dissertation by Drögemöller (2013).*

It is widely conceded that effective treatment in the early stages of the illness is essential for optimising long-term treatment outcome (Amminger et al., 2011; Chiliza et al., 2015). However, this is difficult to achieve as schizophrenia is treated on a trial-and-error basis, which means it may take months to find the right antipsychotic (Yoshida and Müller, 2018; Zhang and Malhotra, 2018). The early identification of poor and non-responders to first-line treatments would enable the expeditious implementation of alternative interventions that are more likely to succeed, thereby preventing accruing morbidity (Chiliza et al., 2015; Emsley et al., 2008). The discovery of reliable predictors of treatment outcome therefore remains a necessity (Emsley et al., 2008; Zhang and Malhotra, 2018). Despite a wealth of large, longitudinal studies dedicated to prognostic factors, very few of the identified outcome predictors have the potential for clinical utility (Carbon and Correll, 2014). Actionable risk factors associated with poor antipsychotic treatment outcomes include longer duration of untreated illness, treatment nonadherence, and lack of early antipsychotic response (Carbon and Correll, 2014; Yildiz et al., 2015). With regard to the first of these, a shorter duration of untreated psychosis (DUP) has been correlated with a shorter time to remission, stable remission, fewer positive symptoms, and better social functioning (Emsley et al., 2008). Additionally, FES patients have demonstrated 57-67% improved response compared to chronic, multi-episode patients (Emsley et al., 2013a). The inverse relationship between DUP

and favourable treatment outcome therefore highlights the importance of early intervention (Emsley et al., 2013a). With regard to treatment adherence, patients whom discontinue their medication have been associated with a five-fold increased risk for relapse, compared to adherent patients (Emsley et al., 2013b; Robinson et al., 2004). An effective strategy to combat this problem has been the introduction of long-acting injectable (LAI) antipsychotics in the place of oral medication (Nasrallah, 2007). Lastly, early treatment response (within the first two weeks) is predictive of favourable outcomes in the long-term, whereas lack of symptom reduction during early stages of treatment is indicative of treatment refractoriness (Emsley et al., 2008). Other predictors of non-response include the male sex, earlier age of onset, poor premorbid adjustment, increased severity of symptoms at baseline, and a lack of insight (Carbon and Correll, 2014; Chiliza et al., 2015).

Overall, the discovery and implementation of antipsychotics for the treatment of schizophrenia has led to radical improvements in the quality of life for countless patients. However, considering the severe ADRs experienced in ~70% of patients (Kahn et al., 2008; Mas et al., 2012), persistence of negative and cognitive symptoms despite continuous treatment, and the high percentage of non-responders, there is a clear need for the discovery of new drug targets and the development of novel treatments for schizophrenia. Furthermore, the heterogeneity observed in antipsychotic treatment response profiles among patients precludes an option for standardised treatment designs for all individuals. Therefore, in addition to implementing reliable clinical predictors of treatment outcome, this emphasises the necessity for determining the underlying biological mechanisms of treatment response in order to develop more individualised treatment strategies.

1.3. Antipsychotic pharmacogenomics

1.3.1. Background

Pharmacogenetics refers to the study of genetic variation contributing to differential drug responses between individuals (Cacabelos et al., 2011; Malhotra et al., 2012). Pharmacogenomics is an expansion of this concept, referring to genetic variation across the entire genome potentially influencing drug response (Cacabelos et al., 2011). With respect to schizophrenia, antipsychotic treatment response is regarded as a complex, multifactorial trait, with a strong genetic basis (Arranz et al., 2011). It has been widely suggested that differential treatment outcomes arise as a result of numerous common variants across the entire genome, each contributing small effect sizes (Arranz et al., 2011). Antipsychotic pharmacogenomics aims to elucidate the genetic underpinnings of differential antipsychotic treatment outcomes in schizophrenia, with the goal of maximising drug efficacy and minimising drug toxicity (Weinshilboum and Wang, 2004; Zhang and Malhotra, 2018).

The first antipsychotic pharmacogenetic studies of schizophrenia made use of candidate gene approaches to investigate treatment outcomes (Arranz et al., 2011). Candidate genes were selected based on their potential involvement in two pharmacological processes, namely pharmacodynamics and pharmacokinetics (Pouget et al., 2014). Pharmacodynamic mechanisms involve the interaction between the drug, transporters, and the receptors or proteins that serve as drug targets (Sandritter et al., 2017; Wijesinghe, 2016). Simply put, pharmacodynamics refers to the effect of the drug on the body. On the other hand, pharmacokinetic processes

can be simply referred to as the effect of the body on the drug, and involve the absorption, distribution, metabolism, and elimination of the drug (Sandritter et al., 2017; Wijesinghe, 2016).

With respect to pharmacodynamic mechanisms, candidate gene studies have largely focussed on dopaminergic and serotonergic neurotransmitter systems (Brandl et al., 2014; Pouget et al., 2014; Yoshida and Müller, 2018). This is expected considering the central role of these systems in antipsychotic mechanism of action. Strong evidence has accumulated for the involvement of variation in genes encoding the dopamine receptors (*DRD2*, *DRD3*, and *DRD4* in particular) and serotonin receptors *(HTR1A* and *HTR2A*) in differential treatment outcomes, including drug efficacy and occurrence of ADRs (Brandl et al., 2014; Pouget et al., 2014; Zhang and Malhotra, 2018). While a number of antipsychotics act on other systems such as adrenergic, muscarinic, and histaminic systems (Correll, 2010), pharmacogenetic studies of these systems have produced inconsistent results, or lack independent replication (Pouget et al., 2014). Considering candidate gene studies of pharmacokinetic processes, genes encoding the cytochrome P450 (CYP) enzyme family have received the most attention (Brandl et al., 2014; Pouget et al., 2014). The CYP enzymes are the most prominent family of drug-metabolising enzymes in humans, and variation within *CYP* genes influences the metabolism of antipsychotic drugs (Arranz et al., 2011; Cacabelos et al., 2011). The differences in metabolism profiles of individuals based on specific *CYP* genotypes range from poor to ultra-rapid metabolisers, with intermediate and normal metabolisers between (Cacabelos et al., 2011). Individuals who are considered poor metabolisers have an increased risk for drug toxicity and developing ADRs, whereas ultra-rapid metabolisers require higher drug dosages to achieve the desired efficacy (Kennedy and Voudouris, 2013). Antipsychotics are predominantly metabolised by CYP1A2, CYP2D6, and CYP2A4, with CYP2C19 influencing the metabolism of clozapine in particular (Pouget et al., 2014). Variation in other *CYP* genes, such as *CYP3A4* and *CYP3A5*, has also been implicated in antipsychotic treatment outcome (Zandi and Judy, 2010).

Early studies of antipsychotic response provided insight with respect to the involvement of numerous candidate genes in treatment outcomes (Yoshida and Müller, 2018). However, none of these findings were sufficiently informative to improve treatment strategies and overall patient outcome, which emphasises the complexity of treatment response. This highlights a necessity for investigating genetic variation in genes beyond those already hypothesised to contribute to drug response via characterised pharmacodynamic and pharmacokinetic processes. The implementation of GWAS for the investigation of antipsychotic treatment outcomes aimed to address this. However, only a handful of antipsychotic response GWAS have been conducted, the majority of which have been hindered by their statistical underpowering owing to limited sample sizes (Allen and Bishop, 2019). Furthermore, there is an overall deficit in the reproducibility of significant findings from these studies. For example, a recent systematic review of GWAS in antipsychotic response reported the identification of 15 genome-wide significant loci across 10 studies, seven of which were replicated in at least one study (Allen and Bishop, 2019). However, only three specific variants were replicated (Allen and Bishop, 2019). While the replication of significant loci may enable further research and contribute to the identification of novel gene targets, the development of pharmacogenetic tests requires extensive replication of specific variants (Allen and Bishop, 2019). In addition to this, the majority of significant GWAS results are located in noncoding regions of the genome (Barešić et al., 2019; Ovenden et al., 2017). These findings often lack sufficient biological interpretation, as most studies tend to focus on the function of adjacent genes without investigating a potential regulatory role of these variants (Barešić et al., 2019; Ovenden et al., 2017). Coupled to this, there has been

minimal functional validation of significant variants identified in noncoding regions, as coding variants have traditionally proven more amenable to functional analyses (Ovenden et al., 2017).

Additional factors that have further hindered cross-study comparisons and replication of findings include varying study designs and differing cohort characteristics (Arranz et al., 2011). For example, variability across cohorts with respect to ethnicity, illness characteristics, type of antipsychotic, treatment duration and adherence, and outcome phenotypes, have restricted interpretation of research findings (Arranz et al., 2011). Overall, numerous genetic variants have been associated with antipsychotic response in the treatment of schizophrenia. However, further well-designed investigations in large, well-characterised cohorts are required to facilitate the progress toward identifying clinically actionable results (Arranz et al., 2011; Yoshida and Müller, 2018).

1.3.2. The South African context

South Africa represents a wide range of population groups, including the more homogeneous Afrikaans speaking Caucasians, the ancient and genetically diverse African populations, and the highly admixed South African Mixed-Ancestry population that has ancestry contributions from African, Asian, and European populations (Daya et al., 2013; Warnich et al., 2011). In the context of genomic research, these populations have unique challenges and advantages, owing to the fact that they harbour the greatest genetic diversity in the world (Warnich et al., 2011). Despite a wealth of antipsychotic pharmacogenomic studies, the vast majority has been conducted in developed countries with individuals of European and Asian descent. African populations therefore remain drastically underrepresented in pharmacogenomic research (Drögemöller et al., 2014). The consequences of this disparity can be demonstrated with the previously discussed *CYP* metaboliser genes as an example (section 1.3.1). A study by Gaedigk and Coetsee (2008) showed that South African Mixed-Ancestry individuals have a unique *CYP* allele composition and a distinct frequency distribution. This was illustrated with the discovery of two novel *CYP2D6* alleles, as well as the vastly different allele frequencies in characterised *CYP* variants compared to individuals of European descent (Gaedigk and Coetsee, 2008). Another study of *CYP* variation by Mitchell et al. (2011) identified 26 novel *CYP2C9* alleles in a cohort of black South Africans. Considering the role of *CYP* genes in the metabolism of antipsychotic and other drugs, fluctuations in enzyme activity arising from differences in *CYP* allele composition and frequencies among population groups has implications in variable treatment response.

With specific reference to antipsychotic pharmacogenomics, Drögemöller et al. (2014) performed exome sequencing on 11 FES patients demonstrating phenotypic extremes for antipsychotic treatment response, i.e. 5 responders and 6 non-responders. The genetic variation was then compared between the two groups to prioritise variants for genotyping in a larger FES cohort (N = 103) and an additional Xhosa schizophrenia cohort (N = 222). Examination of coding variation uncovered loss-of-function variants, most of which were rare or previously unidentified in Asian and European populations (Drögemöller et al., 2014). Furthermore, a potential role of rare loss-of-function variation in treatment response was highlighted, emphasising the importance of conducting population-specific pharmacogenomic research (Drögemöller et al., 2014).

Overall, these studies emphasise the importance of conducting pharmacogenomic research in a South African setting, as genetic associations and clinically actionable findings from more homogeneous populations may not be applicable (Sirugo et al., 2019). Furthermore, the increased levels of genetic diversity and decreased levels of linkage disequilibrium (LD) in South African populations provide a unique and rich resource for better disentangling the genetic underpinnings of complex traits (Ramsay, 2012). This highlights an opportunity to gain novel insight into antipsychotic pharmacogenomics which will not only be beneficial in the progression toward population-specific treatment regimens in a South African context, but in other, less genetically diverse population groups as well.

1.4. Childhood trauma: neuropsychiatric perspectives

1.4.1. Background

Childhood maltreatment can be defined as acts of commission or omission resulting in harm, potential harm, or threat of harm by a parent or caregiver (Sideli et al., 2012). This definition encompasses severe adverse experiences such as physical or emotional abuse and neglect, as well as sexual abuse (Kessler et al., 2010). Childhood maltreatment is a substantial problem worldwide, with estimates suggesting that about a third of the general population may be affected (Kessler et al., 2010). Evidence exists demonstrating that the effects of traumatic experiences during early life may carry through to adulthood, correlating to a range of negative social outcomes including higher criminality, a lower level of education, and decreased overall health and well-being (Varese et al., 2012). Experiences of child maltreatment are highly prevalent among psychosis patients, and have been associated with as much as a three-fold increased risk for developing psychosis (Varese et al., 2012).

Although numerous lines of evidence indicate that childhood trauma may predict an increased risk for the development of psychosis, less is known about the way early life adversities may influence antipsychotic treatment outcomes (Misiak and Frydecka, 2016). However, there is emerging evidence to support a potential role of childhood trauma in treatment response. For example, a study by Hassan and De Luca (2015) reported more frequent experiences of emotional abuse, emotional neglect, and sexual abuse, in treatment refractory patients compared to antipsychotic responders. Additionally, in 2016, Misiak and Frydecka found a link between childhood trauma and early antipsychotic treatment response, suggesting that emotional abuse in particular may contribute to early non-response to treatment in first-episode patients. These two studies therefore show a trend for less favourable treatment response in patients with a self-reported history of childhood trauma. Although, to date, these are the only two studies addressing this issue in schizophrenia, there is evidence for a link between childhood trauma and treatment response in depression. A meta-analysis of 10 clinical trials (3098 participants) revealed that experiences of childhood maltreatment unequivocally predict unfavourable treatment outcome in depression (Nanni et al., 2012). This trend was supported more recently in a large antidepressant response study (1008 participants) of major depression, with childhood trauma predicting poor treatment response (Williams et al., 2016).

Childhood trauma is usually assessed in terms of abuse (physical, sexual, emotional/ psychological) and neglect (physical, emotional/ psychological; Hovdestad et al., 2015). These assessments are done with the

use of self-report questionnaires and semi-structured interviews. The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997) is one of the most frequently used self-report tools in childhood trauma research (Viola et al., 2016). The CTQ comprises 28 items to measure the severity of the aforementioned maltreatment categories, i.e. emotional, physical, and sexual abuse, and emotional and physical neglect. A three-item minimisation/ denial scale is also incorporated to indicate the potential underreporting of maltreatment. Other self-report measurement tools, as recently reviewed by Popovic et al. (2019), include the Personal Safety Questionnaire (PSQ) which is based on the Conflicts Tactics Scales (Straus and Douglas, 2004), the Childhood Sexual Assaults Scale (CSAS; Koss et al., 1987), the Early Trauma Inventory Self Report (ETI-SR; Bremner et al., 2007), the Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000), and the Adverse Childhood Experiences (ACE) questionnaire (Felitti et al., 1998). Semi-structured interviews include the Early Trauma Inventory (Bremner et al., 2000) and the Children's Life Events Scale (CLES), which is an expansion of the Source of Stress Inventory (Chandler, 1981).

1.4.2. Gene-environment interactions (GxE)

Although a history of childhood trauma appears to substantially increase the risk for psychosis, childhood maltreatment is by no means causal, as it is neither necessary, nor sufficient, to give rise to the onset of psychosis (Misiak et al., 2017). Considering the evidence for the substantial heritability of schizophrenia, it is probable that the relationship between childhood trauma and schizophrenia is mediated by gene-environment interactions (GxE; Misiak et al., 2017). In other words, the effect of childhood trauma on disorder manifestation is contingent on differences in genetic factors, and vice versa (Assary et al., 2018). This is supported by several studies of the risk or clinical manifestation of schizophrenia, whereby the effects of childhood trauma appear to be moderated by differences in genotype for candidate variants (Alemany et al., 2015; Collip et al., 2013; Green et al., 2014; 2015; Modinos et al., 2013). One example is the study by Green et al. (2014), where *COMT* Val/Met heterozygotes with a history of physical abuse had more severe positive symptoms, and more severe negative symptoms were found in *COMT* Val/Met heterozygotes that had experienced emotional neglect. Additionally, the same study identified a significant interaction whereby emotional neglect was associated with increased severity of negative symptoms in *COMT* Met/Met homozygotes (Green et al., 2014). There is also emerging evidence for the role of GxE with childhood trauma in differential response to antipsychotics in schizophrenia. McGregor et al. (2018) reported that associations between *MMP9* variants and antipsychotic treatment response were modified by childhood trauma. For example, the homozygous recessive (*AA*) genotype for *MMP9* rs13925 conferred improved response to antipsychotics when childhood trauma was not considered (McGregor et al., 2018). However, when the severity of childhood trauma was factored in as an interacting variable, poor response to antipsychotic treatment was observed in these individuals in the presence of emotional neglect (McGregor et al., 2018). These findings lend support to the role of childhood trauma in antipsychotic treatment response, possibly via interactions with genetic factors. Although only one such study could be identified for treatment response in schizophrenia, this type of research has shown promise for treatment response in depression. Here, studies have shown that interactions between early life adversity and polymorphisms in serotonergic, glutamatergic, and GABAergic genes, influence antidepressant drug response (Pu et al., 2013; Xu et al., 2012). Altogether, these findings necessitate further investigation of GxE with childhood trauma in antipsychotic treatment response, as potentially crucial mechanisms underlying treatment outcomes could be uncovered.

The complex interaction between genetic and environmental factors is mediated by epigenetic mechanisms (Petronis, 2010). These include DNA methylation, histone modifications, and regulation brought about by microRNAs (miRNAs) and other noncoding RNA molecules (Kuehner et al., 2019). These mechanisms bring about heritable alterations in gene expression and regulation, without modifying the DNA sequence itself (Kuehner et al., 2019). Epigenetic regulation is crucial in neurodevelopment, where it has implications in brain growth, neuronal and synaptic plasticity, learning, and memory (Fagiolini et al., 2009; Ovenden et al., 2018). For these reasons, it is not surprising that epigenetic dysregulation has been implicated in the development of neuropsychiatric disorders, including schizophrenia (reviewed by Ptak and Petronis, 2010). Although in its infancy, pharmacoepigenomics aims to characterise the influence of epigenetic alterations on differential drug response and holds much potential to explain the missing heritability observed in antipsychotic treatment outcomes (Ovenden et al., 2018; Zhang and Malhotra, 2018).

Although current research pertaining to childhood trauma in antipsychotic treatment response (including GxE and epigenetic alterations) is limited, there is emerging evidence to support the role of childhood trauma as a relevant modifier of treatment outcomes in schizophrenia (McGregor et al., 2018). The importance of pursuing this line of research is highlighted by the opportunity it presents for additional therapeutic considerations (Gianfrancesco et al., 2019). Firstly, considering the potential contributions of childhood trauma to differential treatment response phenotypes via interactions with genetic elements, it has been suggested that trauma-exposed individuals may represent a biologically distinct subtype of patients that require different therapeutic interventions to patients not exposed to severe trauma (Teicher and Samson, 2013). Secondly, awareness of the effects of childhood trauma will support a movement toward trauma-informed treatment approaches and psychological therapy-based interventions (Gianfrancesco et al., 2019). Overall, better characterising the role of childhood trauma in antipsychotic treatment response along with the underlying mechanisms mediating this relationship may help to guide and improve treatment strategies in the future based on multifaceted patient profiles, including information on genetic, epigenetic, and environmental elements.

1.5. Imaging genetics in neuropsychiatric disorders

1.5.1. Background

Existing neuroimaging methods can broadly be divided into those that examine structural aspects and those that examine functional aspects of the brain (Kovelman, 2012). Structural imaging methods include computed tomography (CT), structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI); functional imaging methods include functional MRI (fMRI), arterial spin labelling (ASL), positron emission tomography (PET), and single photon emission computed tomography (SPECT; Kovelman, 2012). Imaging genetics is a relatively new and rapidly progressing field that integrates neuroimaging and genetic data to investigate the genetic architecture of varying brain phenotypes, most frequently based on MRI and fMRI measurements (Mufford et al., 2017; Turner et al., 2006). Although this in itself encompasses an extensive range of research, one of the most important applications of the field is the study of neuropsychiatric disorders (Hashimoto et al., 2015). The implementation of imaging genetics approaches for the investigation of neuropsychiatric disorders is based on the premise that variations in brain structure and function are so-called “intermediate phenotypes”, or endophenotypes, that lie closer in the biological trajectory of genes than the psychiatric disorder itself

(Meyer-Lindenberg and Weinberger, 2006). An endophenotype can be broadly defined as a measurable and heritable trait that is genetically correlated with a disorder (Gottesman and Gould, 2003). Considering that differential phenotypic definitions may result in different genetic associations, the subjective nature of complex psychiatric disorder diagnoses may be one of the factors hindering the effective elucidation of these disorders (Greenwood et al., 2019). As the measurement of brain imaging phenotypes is more objective, these endophenotypes may serve as biological proxies for disorder manifestation, potentially accelerating the discovery of important disorder risk variants (Greenwood et al., 2019). Aside from the potential contribution to the discovery of genetic variants implicated in psychiatric disorders, imaging genetics will likely provide critical insight into the neurobiological mechanisms underlying these complex disorders (Figure 1.3; Greenwood et al., 2019; Iacono et al., 2014). Overall, this research aims to improve the understanding of psychiatric disorders in terms of symptoms and aetiology, to prognosis and treatment, with the goal of identifying reliable biomarkers and improving diagnostic assessments and treatment strategies (Mufford et al., 2017).

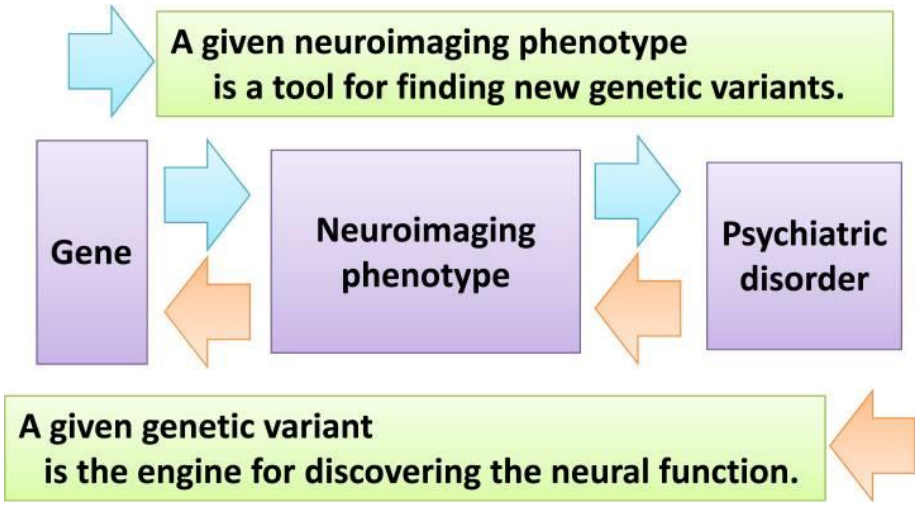


Figure 1.3. Two applications of imaging genetics in the context of psychiatric disorder research (Hashimoto et al., 2015). *Reproduced from Hashimoto et al. (2015), as per the following license: https://creativecommons.org/licenses/by-nc/3.0/legalcode*.

The field of imaging genetics was first introduced approximately 20 years ago with twin and family studies aiming to calculate the heritability estimates for neuroimaging-based measurements such as brain volume (Bartley et al., 1997), shape (Ge et al., 2016; Roshchupkin et al., 2016), activity (Glahn et al., 2010), connectivity (Jahanshad et al., 2013), and white matter microstructure (Patel et al., 2010). These studies confirmed that certain brain measures derived from non-invasive scans have a moderate to strong genetic basis, which is an important property in the selection of appropriate endophenotypes (Gottesman and Gould, 2003). Early imaging genetics studies of psychiatric disorders made use of hypothesis-driven, candidate gene approaches to investigate associations between well-characterised genetic variants and brain structural or functional phenotypes (Mufford et al., 2017). Toward the end of the first decade of imaging genetics research in psychiatric disorders, methodologies expanded from candidate gene approaches to investigations of gene-gene interactions (Figure 1.4; Mufford et al., 2017). From 2011, imaging genetics studies started to incorporate GxE and epigenetic effects. During the first 10 years, hypothesis-free approaches, i.e. GWAS, were implemented, along with the emergence of large-scale collaborations and consortia (Mufford et al., 2017). Examples of such consortia include the Enhancing NeuroImaging Genetics through Meta-analysis (ENIGMA)

consortium (Thompson et al., 2014; http://enigma.ini.usc.edu/), Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (Psaty et al., 2009; http://web.chargeconsortium.com/), and the IMAGEN study (Schumann et al., 2010; https://imagen-europe.com/). With the advent of big data came the development of multivariate approaches to account for arising statistical challenges. Additionally, GWAS of neuropsychiatric disorders revealed significant variants with previously uncharacterised biological roles, which therefore warranted investigation using candidate imaging genetics approaches. The most recent developments in the imaging genetics field include the expansion of hypothesis-free approaches to alternative genetic models such as gene-gene interactions (Mufford et al., 2017).

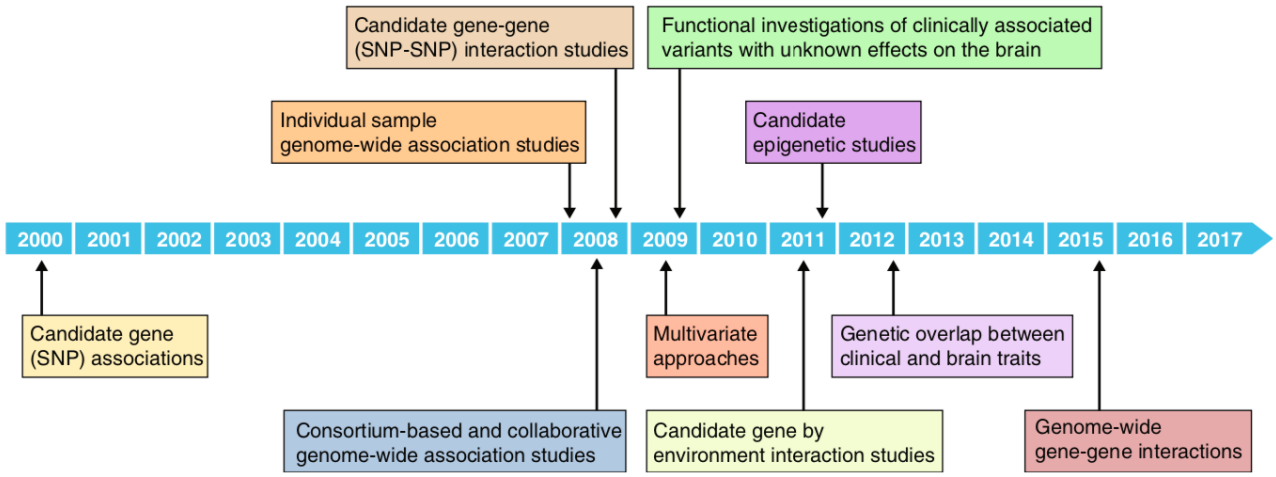


Figure 1.4. A timeline of methodological approaches implemented in imaging genetics studies of neuropsychiatric disorders (Mufford et al., 2017). *Reproduced from Mufford et al. (2017), as per the following license: https://creativecommons.org/licenses/by-nc/3.0/legalcode.*

1.5.2. Imaging genetics in schizophrenia and antipsychotic response

A multitude of studies over the last two decades has been dedicated to investigating the imaging genetics of schizophrenia (Greenwood et al., 2019). These studies have revealed promising findings in terms of the genetic contributions to certain brain structural and functional correlates of the disorder (Greenwood et al., 2019). Numerous widely studied genes implicated in schizophrenia, such as *AKT1*, *BDNF*, *COMT*, *DISC1*, *DTNBP1*, and *NRG1*, have been investigated in imaging genetics studies (Hashimoto et al., 2015). The *COMT* gene has been the most frequently studied of these genes in both structural and functional imaging genetics studies of schizophrenia (Meyer-Lindenberg, 2010). A meta-analysis of all the functional neuroimaging studies of *COMT* rs4680 that were done before 2008 found that this variant has a significant impact on prefrontal activation (Mier et al., 2010). Findings relating to the effects of *COMT* variation on brain structure have been less consistent than functional findings (Meyer-Lindenberg, 2010), but one example is a study of *COMT* rs4680 that found significant volumetric reductions in the bilateral anterior cingulate cortex (ACC), left amygdala-uncus, right middle temporal gyrus (MTG) and left thalamus, in schizophrenia patients with the homozygous Val/Val *COMT* genotype compared to *COMT* Met carriers (Ohnishi et al., 2006). No significant genotype effects on brain morphology were found in the control group, which suggests that *COMT* rs4680 might contribute to morphological abnormalities in schizophrenia (Ohnishi et al., 2006). In terms of schizophrenia imaging genetics studies in the post-GWAS era, significant variants identified in schizophrenia GWAS have been found to impact various structural phenotypes (reviewed by Gurung and Prata, 2015). These include grey matter volume

(variants in *CACNA1C*, *NRGN*, *TCF4* and *ZNF804A*), ventricular volume (*TCF4*), cortical folding (*NCAN*) and thickness (*ZNF804A*), white matter integrity (*ANK3* and *ZNF804A*), white matter volume (*CACNA1C* and *ZNF804A*) and white matter density (*ZNF804A;* Gurung and Prata, 2015).

Despite the extensive imaging genetics research in schizophrenia, studies of this nature investigating antipsychotic treatment outcomes remain scarce. Furthermore, to our knowledge, all of the imaging genetics studies of antipsychotic response thus far have only focussed on fMRI measurements, and no studies have investigated the genetic underpinnings of structural brain measurements in antipsychotic response. In a study by Blasi et al. (2011), the interaction between specific *DRD2* and *AKT1* variants was associated with altered cingulate response and reduced behavioural accuracy during attentional processing in healthy individuals, and with greater PANSS score improvement in patients treated with olanzapine. In a later study by Blasi et al. (2015), it was found that combined effects of *DRD2* and *HTR2A* variants may influence working memory processing reflected by prefrontal activity in healthy individuals, as well as response to antipsychotic treatment in patients with schizophrenia. Lastly, in a group of patients with schizophrenia, variants in *GRM3* were associated with a reduction in negative symptoms as well as a worsening of working memory deficits after antipsychotic treatment (Bishop et al., 2015). Therefore, despite apparent symptom improvement, these results suggested that *GRM3* variants may influence the risk for adverse cognitive effects of antipsychotic treatment (Bishop et al., 2015).

Overall, these studies highlight the potential utility of imaging genetics to improve our understanding of the underlying mechanisms relating to antipsychotic treatment and response. However, two of the three studies investigated the genetics of neuroimaging phenotypes in healthy individuals, and compared these findings to treatment response measurements in schizophrenia patients (Blasi et al., 2011; 2015). This highlights a clear deficit in research addressing the genetic components of neuroimaging phenotypes in direct relation to antipsychotic response, i.e. conducting both the imaging genetics analysis and the pharmacogenetics analysis in the patient cohort. Even though the third study identified a potential genetic subgroup of patients that may have a greater risk for adverse cognitive effects in relation to antipsychotic treatment (Bishop et al., 2015), of potentially greater value would be the use of imaging genetics approaches for the identification of baseline (pre-treatment) neuroimaging phenotypes that have the capacity to reliably predict treatment outcome in certain patients based on genetic profiles (Kempton and McGuire, 2015). This would enable the implementation of more guided treatment strategies based on predictive response profiles derived from individual-level genetic data combined with neuroimaging data. In order to address this, imaging genetics studies of antipsychotic response should be done with both MRI and fMRI correlates, as both structural and functional brain measurements would be valuable in the search for robust and reliable biomarkers of treatment response. In fact, it is surprising that none of the existing imaging genetics studies of antipsychotic response have included structural neuroimaging phenotypes, as the existing literature on neuroimaging studies of antipsychotic response includes a greater number of studies that focussed on structural neuroimaging measures compared to functional modalities (reviewed by Tarcijonas and Sarpal, 2019). These structural imaging studies have found correlations between numerous brain regions and response to antipsychotic treatment, considering various measurements such as thickness, volume, and density (Tarcijonas and Sarpal, 2019). For example, increased hippocampal volumes have been associated with favourable response to risperidone treatment (Savas et al., 2002), and increased thickness of temporal regions have been associated

with more rapid response to antipsychotic treatment (Szeszko et al., 2012). These findings highlight the potential for structural brain measurements as useful intermediate phenotypes of antipsychotic response in imaging genetics studies moving forward.

1.5.3. Imaging gene-environment interactions (iGxE)

Examining the interplay between genes, experience and the brain is essential to improve our understanding of psychopathology. In this regard, both gene-environment interaction studies and imaging genetics studies have shown much promise in the study of neuropsychiatric disorders (as discussed in sections 1.4.2, 1.5.1, and 1.5.2.). However, these approaches have very rarely been integrated, despite their considerable potential to inform each other. Recognising this potential, Hyde et al. (2011) proposed the term imaging gene-environment interactions (iGxE) to describe an integrative research strategy combining gene-environment interactions and imaging genetics. The authors of this review state that "Overall, iGxE can provide a more nuanced and complex model of human nature in health and disease by extending beyond nature–nurture debates and revealing specific mechanisms through which the constantly interacting environment and genome can be understood at the level of brain function and behaviour" (Hyde et al., 2011). Considering an iGxE model of a complex neuropsychiatric disorder, there are numerous ways in which genetic, neural, environmental, and behavioural factors could interact (Figure 1.5).

Although iGxE approaches have not been implemented for the investigation of antipsychotic treatment response, this approach has been used in the context of healthy individuals (Gerritsen et al., 2011), major depressive disorder (Carballedo et al., 2013; Frodl et al., 2014), and schizophrenia (Aas et al., 2013). For example, Aas et al. (2013) found that *BDNF* rs6265 modulated the association between childhood trauma and brain cognitive and structural abnormalities in psychosis. Specifically, Val/Met individuals exposed to high levels of childhood abuse showed poorer cognitive functioning compared to homozygous Val/Val individuals (Aas et al., 2013). Additionally, reduced right hippocampal volumes and larger right and left lateral ventricles were observed in Val/Met individuals with a history of severe sexual abuse (Aas et al., 2013).

The goals of personalised treatment approaches in psychiatry are to predict the risk of developing a psychiatric disorder, obtain an accurate diagnosis, and predetermine the most effective therapeutic strategy for an individual (Ozomaro et al., 2013). Despite decades of research in numerous fields (i.e. genetic, neuroimaging, and clinical studies) aimed at elucidating the mechanisms contributing to differential antipsychotic treatment outcomes with the goal of progressing toward more personalised treatment regimens, the clinical utility of research findings thus far remains incredibly limited. It is therefore plausible that embracing more integrated research approaches may better inform on the relationships between correlates of treatment response, and more effectively disentangle the mediating factors and mechanisms underlying these relationships (Cao et al., 2014; Domschke and Müller, 2015). Specifically, an iGxE approach considering the interplay between genetic, neuroimaging, and environmental factors may be a reasonable starting point. Firstly, not only have genetic variants and childhood trauma been associated with differential treatment outcomes in schizophrenia, respectively, but a potential role of GxE with childhood trauma in antipsychotic response has also been highlighted. Secondly, the same can be said for variations in brain structural and functional phenotypes. Lastly, structural and functional brain measurements have been implicated in differential response to antipsychotic

treatment. Therefore, the existing literature addressing the various relationships between genetic factors, brain imaging phenotypes, childhood trauma, and treatment outcomes in schizophrenia, points to the potential utility of integrated iGxE studies of antipsychotic response.

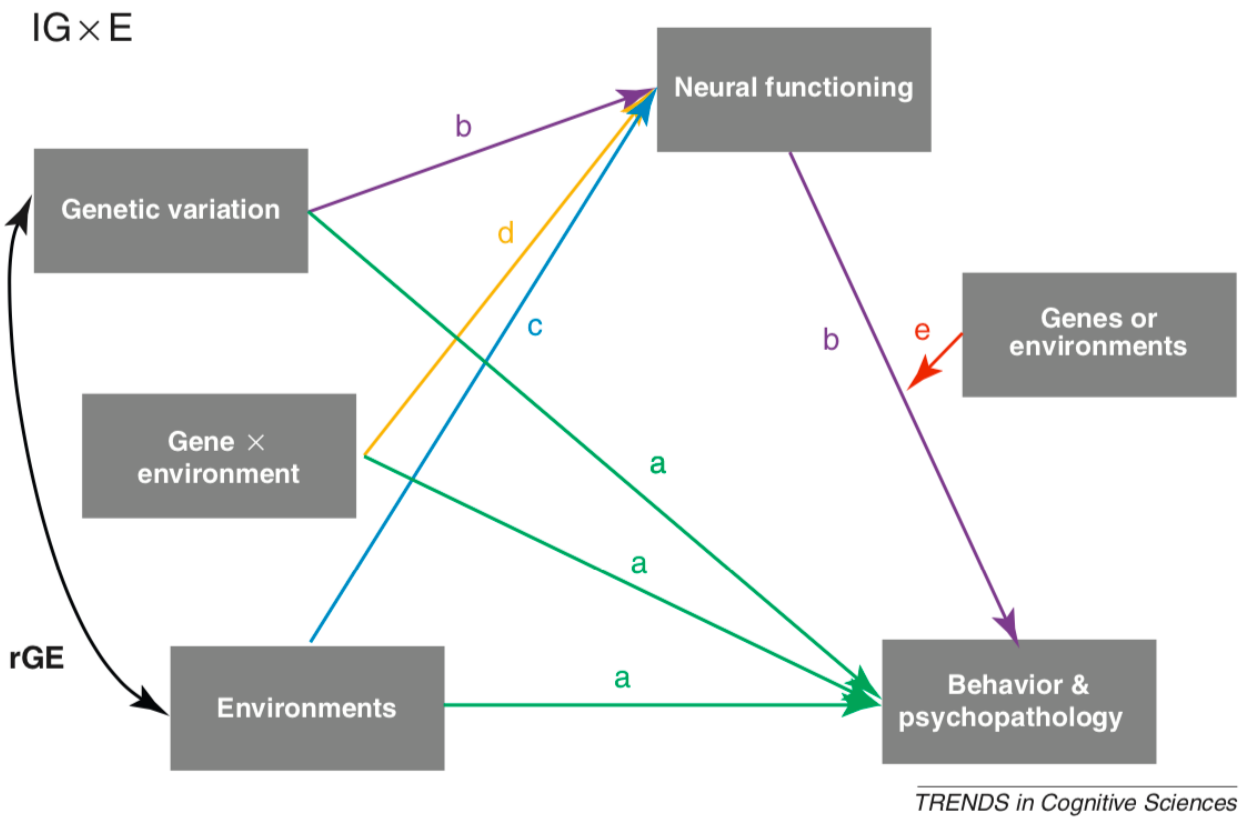


Figure 1.5. A conceptual model of iGxE (Hyde et al., 2011). Traditional GxE and imaging genetic paths are highlighted among the variables, as well as new potential paths for iGxE studies. The 'a' paths (green) demonstrate typical GxE relationships; 'b' paths (purple) model traditional links in imaging genetics approaches; the 'c' path (blue) models the direct effect of the environment on neural functioning (as demonstrated in epigenetic studies); the 'd' path (yellow) models GxE prediction of neural functioning (the iGxE effect); the 'e' path (red) represents the possibility of genetic variation or environmental variables interacting with neural functioning to predict behaviour. Indirect and mediated pathways can be connected between many of the variables (e.g. GxE to behaviour via neural functioning). rGE = gene-environment correlation. An ideal iGxE finding would be a GxE interaction term that predicts behaviour through neural functioning. *Reproduced with permission from Elsevier*.

1.6. Overview of the current study

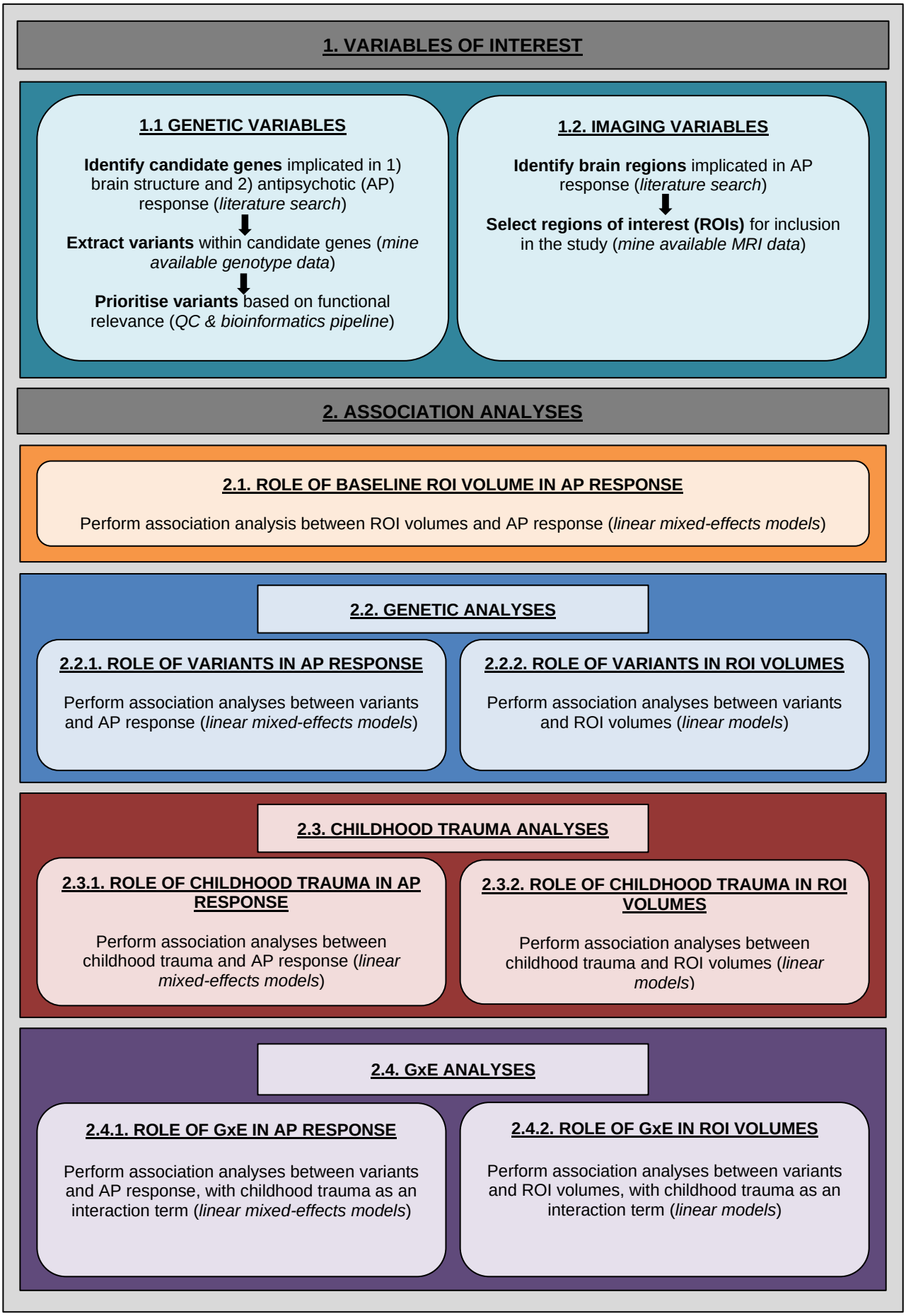
1.6.1. Aim and objectives

This study aims to investigate the interplay between genetics, childhood trauma, and brain structure, in the context of antipsychotic treatment response, using an integrative research approach.

The aforementioned aim will be achieved by the following objectives:

1. To determine whether volumetric variation in brain regions previously associated with antipsychotic response are associated with treatment outcomes in a South African FES cohort.
    a. Survey the literature to identify brain regions that have been previously implicated in antipsychotic response.
    b. Conduct association analyses to investigate whether volumetric variation in any of these regions is associated with antipsychotic response in a local cohort.
2. To determine whether candidate genes previously implicated in both brain structure and antipsychotic response are associated with brain structure and antipsychotic treatment response in a South African FES cohort.
    a. Search the literature for genes shown to influence both brain structure and antipsychotic response.
    b. Make use of publicly available data and bioinformatics tools to identify functionally relevant variants within these genes.
    c. Perform association analyses to investigate the involvement of these prioritised variants in brain structure and antipsychotic treatment response.
3. To determine whether childhood trauma severity is associated with brain structure and antipsychotic treatment response.
    a. Conduct association analyses to determine the influence of the severity of childhood trauma on both brain structure and antipsychotic treatment response.
4. To determine wther GxE are associated with brain structure and antipsychotic treatment response.
    a. Perform association analyses to determine if any GxE between childhood trauma and prioritised genetic variants are associated with brain structure or antipsychotic treatment response.

1.6.2. Strategy



CHAPTER 2

Materials and methods

2.1. Role of the incumbent

Clinical interviews, patient treatment, data collection, MRI scans, and blood sampling, were performed by trained clinicians. Neuroimaging data was generated by experts in the field at the University of Stellenbosch, Tygerberg Medical Campus. DNA extractions were performed by a laboratory technician. Genotyping was performed prior to this study by the Department of Psychiatry, Zucker Hillside Hospital, New York, USA. The role of the incumbent of this study was therefore to make use of existing literature to select candidate genes and brain regions of interest to include in the study. The incumbent then mined existing neuroimaging data provided to identify available brain regions of interest, and extracted all of the genetic variants within the selected candidate genes from the genome-wide genotype data provided. The incumbent then designed and subsequently implemented a novel bioinformatics pipeline to prioritise genetic variants, making use of a number of online databases and *in silico* prediction tools. In addition to this, the incumbent wrote several R scripts in RStudio, making use of linear regression and mixed-effects modelling to execute the necessary association analyses between all variables of interest, in line with the aim and objectives of the study. Model diagnostics were also performed by the incumbent for all analyses in RStudio. The results were then discussed and conclusions were drawn by the incumbent within this thesis.

2.2. Participants

The patient cohort comprised 103 unrelated South African individuals (median age 23 ± 7 years; 76 males and 27 females) who were recruited through Stikland Hospital in the Western Cape, between April 2007 and March 2011, as described previously (Chiliza et al., 2015; Drögemöller et al., 2014; Emsley et al., 2015; Emsley et al., 2017). Of these participants, 82 were South African Mixed-Ancestry, 13 were Xhosa, and 8 were of Caucasian descent as per self-reported ancestry. Inclusion criteria for the study were men and women between the ages of 16 and 45, experiencing a first episode of psychosis according to the diagnostic criteria for schizophrenia, schizophreniform, or schizoaffective disorder as defined by the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV; American Psychiatric Association, 1994). Exclusion criteria were exposure to more than four weeks of antipsychotic medication during participants' lifetime, any previous treatment with a long-acting depot antipsychotic, serious or unstable general medical condition, intellectual disability, and overt substance abuse. Clinical and demographic data were obtained for all participants at the time of recruitment. Written informed consent was received from the participants or their caregivers, and from the legal guardian in the case of minors. Ethical approval was obtained from the Human Research and Ethics Committee (HREC), Faculty of Health Sciences, University of Stellenbosch (N06/08/148).

2.3. Clinical assessments

At the time of recuitment, all participants were assessed by means of the Structured Clinical Interview for DSM-IV (SCID; American Psychiatric Association, 1994). They were also scored in terms of symptom severity

according to the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) before receiving treatment, and then every two weeks for the first six weeks, and every three months thereafter, for a period of 12 months. Symptoms were categorised into either positive, negative, or general symptom domains, and participants were given a score for each separate symptom category, as well as a total score. The change in positive, negative, general, and total PANSS scores over 12 months was used to indicate drug efficacy and response to antipsychotic treatment. The Clinical Global Impressions (CGI) Scale (Busner and Targum, 2007) was also used to monitor treatment response over time. Extrapyramidal symptoms were examined using an Extrapyramidal Symptom Rating Scale (ESRS; Chouinard and Margolese, 2005). The CTQ (Bernstein et al., 1997) was used to evaluate the type and severity of childhood trauma in 75 of the participants according to the five subscales, namely emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Scores for the five subscales were summed to obtain an overall trauma (CTQ total) score for each participant. A minimisation/ denial scale was also incorporated to indicate inaccurate reporting of mistreatment. Substance abuse was measured with a structured substance abuse questionnaire.

2.4. Treatment

All participants were treated according to a standardised protocol with flupenthixol decanoate (a first-generation antipsychotic) in the form of a long-acting injectable, thereby ensuring adherence (Chiliza et al., 2015). A 1-3 mg/day dosage of oral flupenthixol was administered for the first week, followed by fortnightly injections of flupenthixol depot, at a starting dose of 10 mg every two weeks, with increments of 10 mg permitted every six weeks, to a maximum of 30 mg fortnightly (Chiliza et al., 2015). The lowest possible dose of the antipsychotic was maintained, only increased when insufficient response persisted (less than 20% reduction in the PANSS total score, and minimal improvement on the CGI Scale), until either remission was achieved – as defined by the Remission in Schizophrenia Working Group (Andreasen et al., 2005) - or the maximum allowed/ tolerated dose was reached (Chiliza et al., 2015). Early response to treatment was indicated by a ≥ 25% reduction in PANSS total scores within the first six weeks. Non-response was defined by either a discontinuation of treatment due to poor response, a < 25% reduction in PANSS total scores at end-point, or a PANSS total score of > 70 at end-point (Chiliza et al., 2015).

2.5. Neuroimaging variables

2.5.1. Imaging methods

A subset of participants (N = 76) underwent baseline MRI scans prior to antipsychotic treatment, at the time of recruitment. The following imaging methods were used, and have been described previously (Emsley et al., 2015; Emsley et al., 2017). High-resolution T1-weighted data were obtained using a 3T Siemens Allegra MRI scanner (Erlangen, Germany) with the following acquisition parameters: MPRAGE sequence, 2080 ms repetition time; 4.88 ms echo-time, field of view: 230 mm, 176 slices, voxel size: 0.9 × 0.9 × 1 mm^3. All scans were screened for intracranial pathology and motion artefacts, and were processed and analysed using Freesurfer version 6.0.0. Slices were resampled to a three-dimensional image with 1 mm isotropic voxels. Non-uniform intensity normalisation was performed, and images were registered to the Montreal Neurological Institute space. A second normalisation step was then performed, where control points were automatically

identified and normalised to a standard intensity value. This was followed by an automated skull strip procedure. Global brain anatomy was delineated into cortical and subcortical labels. Reconstructions were performed with custom batching scripts, on the Centre for High Performance Computing, Cape Town, Lengau cluster. All data were visually inspected for errors in Talairach transformation, skull strip, final segmentations and within subject-registrations. Detailed quality-checking was done, whereby errors were manually corrected and re-inspected. This resulted in 74 participants with usable baseline MRI data, which was available prior to the current study.

2.5.2. Brain regions of interest (ROIs)

A literature search was performed via PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and the Stellenbosch University Library to identify brain regions of interest (ROIs) that had been previously implicated in variable response to antipsychotic treatment. This search was conducted between March and May 2018, using combinations of the following search terms: “brain”, “imaging”, “morphology”, “morphometry”, “MRI”, “neuroanatomical”, “neuroimaging”, “region”, “structural”, “structure”, “variation”, “volume”, “volumetric”, “voxel”, “antipsychotic”, “first episode”, “outcome”, “psychosis”, “psychotic”, “resistant”, “response”, “schizophrenia”, “treatment”. Only measures of volume were considered for the study, as volumetric measurements were the most abundant in both the literature and the available structural MRI data. The available MRI data was mined for the ROIs that were identified in the literature search (i.e. previously associated with antipsychotic treatment response). Eight ROIs were identified in the available MRI data, and were thus included in the study. The volumetric measurements for the ROIs were expressed as percentages of total intracranial volume.

2.6. Genetic variables

2.6.1. DNA extraction and genotyping

Whole blood samples were previously obtained from all 103 participants using venepuncture, from which genomic DNA (gDNA) was isolated using the Miller *et al*. (1988) protocol. Prior to this study, the entire cohort was genotyped using the Infinium OmniExpressExome-8 Kit (Illumina, California, USA), that includes 958,497 SNP markers.

2.6.2. Candidate gene selection

A literature search was performed *via* PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and the Stellenbosch University Library to identify genes that had been previously implicated in both brain structure and antipsychotic treatment response. This search was conducted between March and May 2018, using combinations of the following search terms: “gene”, “genetic”, “genome-wide association study”, “GWAS”, “pharmacogenetic”, “pharmacogenomic”, “polymorphism”, “SNP”, “variation”, “brain”, “imaging”, “morphology”, “morphometry”, “MRI”, “neuroanatomical”, “neurodevelopment”, “neuroimaging”, “region”, “structural”, “structure”, “variation”, “volume”, “volumetric”, “voxel”, “antipsychotic”, “first episode”, “outcome”, “psychosis”, “psychotic”, “resistant”, “response”, “schizophrenia”, “treatment”. Inclusion criteria for genes implicated in brain structure required that

the studies involved neuroimaging measures of volume only, in either healthy individuals, or individuals with schizophrenia (no other disorders); and inclusion criteria for genes implicated in antipsychotic treatment response required that the studies involved any measure of response to any antipsychotic in individuals with schizophrenia (no other neuropsychiatric disorders), excluding measurements of any antipsychotic-induced adverse drug reactions. Following the literature search, the NHGRI-EBI GWAS Catalog (MacArthur et al., 2017), which is a curated collection of all published genome-wide association studies, was searched for GWAS of brain structure and antipsychotic treatment response, in May 2018. The term “brain volume measurement” was used to identify studies of brain structure, and the term “response to antipsychotic drug” was used to identify studies of antipsychotic treatment response. Inclusion criteria for GWAS were the same as for studies identified in the literature search, outlined above. No studies that considered the genetics of brain structure in the context of antipsychotic treatment response were identified, therefore two separate gene lists were compiled for 1) implication in brain structure and 2) implication in antipsychotic response. Each of the genes in these two lists were then cross searched with the other trait, to ensure no relevant studies were missed. Genes identified in both lists were selected as candidate genes for the study.

2.6.3. Variant prioritisation

PLINK v1.9 (Purcell et al., 2007) was used to mine the available genome-wide genotype data for variants within the identified candidate genes, using the positions documented on each gene page of the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/gene/) for the GRCh37.p13 genome assembly. Variants 1000 bp up- and downstream from each gene were also extracted to account for additional non-coding variation for these genes. Allele frequencies for each variant were extracted using PLINK v1.9 (Purcell et al., 2007). Choosing to focus on the effects of common variants, all variants were then filtered according to minor allele frequency (MAF) in order to eliminate rare variants. Variants with an MAF of ≥ 0.1 were considered as “common” and were selected for further analyses. In order to further prioritise variants for inclusion in the study, these variants were investigated for previously reported implication in antipsychotic treatment response and brain structure, and predicted functional consequences or regulatory effects, with the use of various online databases and *in silico* prediction tools. The databases and tools used are summarised in Table 2.1, along with the type of prediction for each, and the dates accessed.

The following describes the prioritisation process and criteria for inclusion of variants in the study: Variants that had been previously associated with either brain structure or antipsychotic treatment response in the literature were included for further analyses. The NHGRI-EBI GWAS Catalog (MacArthur et al., 2017) was used to investigate whether any of the variants had been significantly associated with either brain structure or antipsychotic treatment response in relevant GWAS. PharmGKB (Whirl-Carrillo et al., 2012) is a resource that curates knowledge about the effects of genetic variation on drug response. Variants that were shown to have an effect on antipsychotic efficacy, toxicity or response (including adverse drug reactions) according to the clinical and variant annotations on PharmGKB were included. In order to investigate predicted functional consequences of all variants, Ensembl (Zerbino et al., 2018), SNPnexus (SIFT and Polyphen options, for assembly GRCh38/hg38; Chelala et al., 2009), SIFT (Sim et al., 2012) and Polyphen-2 (Adzhubei et al., 2010) were used. Variants reported to be missense, nonsynonymous, deleterious, damaging, probably damaging, or possibly damaging, according to any of these databases/ tools were included. The potential regulatory

impact of variants was also investigated with the use of SNPnexus (TarBase option, for assembly GRCh38/hg38; Chelala et al., 2009), PolymiRTS (Bhattacharya et al., 2014), SNP2TFBS (Kumar et al., 2017), RegulomeDB (Boyle et al., 2012), and rSNPBase (Guo et al., 2014). Any variants reported as having a potential impact on a miRNA target site according to SNPnexus (TarBase option), or on miRNA binding according PolymiRTS, were included. Variants shown to affect transcription factor binding according to SNP2TFBS were included for downstream analyses. Lastly, variants with scores ranging from '1a' to '3b' as per the RegulomeDB scoring system (outlined in Table S1) were included. As almost all variants were reported as rSNPs (regulatory single nucleotide polymorphisms) according to rSNPBase, this information was not used in the prioritisation process, as very few variants would have been eliminated. However, rSNPBase was still used in the annotation of all variants for future reference. This informs on the role of each variant in regulation of a proximal, distal, miRNA and/ or RNA binding protein mediated nature, as well as reported eQTL (expression quantitative trait loci) status. This pipeline resulted in 192 variants that were prioritised for inclusion in the study.

2.6.4. Variant descriptive statistics

PLINK v1.9 (Purcell et al., 2007) was used to assess Hardy-Weinberg equilibrium (HWE) for the prioritised variants (significance threshold of $P \leq 0.01$). SNPStats (Sole et al., 2006) was used to determine genotype frequencies, and to assess levels of LD between the prioritised variants for each gene. This was based on the D' statistic, where values above 0.8 were indicative of strong LD.

Table 2.1. Summary of online databases and tools used for variant prioritisation.

Online database/tool	Option/tool used	Variant prediction type	Link	Reference	Date accessed
Ensembl	Variant Effect Predictor	Functional impact	https://www.ensembl.org/	(Zerbino et al., 2018)	June 2018
PolyPhen-2	*NA*	Functional impact	http://genetics.bwh.harvard.edu/pph2/	(Adzhubei et al., 2010)	May 2018
SIFT	SIFT dbSNP	Functional impact	https://sift.bii.a-star.edu.sg/	(Sim et al., 2012)	May 2018
SNPnexus[1]	SIFT PolyPhen TarBase	Functional impact Functional impact Impact on miRNA target site	https://snp-nexus.org/	(Chelala et al., 2009; Ullah et al., 2012, 2013, 2018)	May 2018
PolymiRTS	*NA*	Impact on miRNA binding	http://compbio.uthsc.edu/miRSNP/	(Bhattacharya et al., 2014)	June 2018
SNP2TFBS	SNPViewer	Impact on TF binding	https://ccg.epfl.ch/snp2tfbs/	(Kumar et al., 2017)	June 2018
RegulomeDB	*NA*	Regulatory impact	http://regulome.stanford.edu/	(Boyle et al., 2012)	May 2018
rSNPBase	*NA*	Regulatory impact	http://rsnp.psych.ac.cn/	(Guo et al., 2014)	May 2018
PharmGKB	Clinical and Variant Annotations	Impact on drug efficacy/ response	https://www.pharmgkb.org/	(Whirl-Carrillo et al., 2012)	August 2018
NHGRI-EBI GWAS Catalog	*NA*	Implication in brain structure/ antipsychotic response	https://www.ebi.ac.uk/gwas/	(MacArthur et al., 2017)	August 2018

TF = Transcription factor
[1]Using annotation categories for GRCh38/hg38

2.7. Association analyses

All association analyses that were done for this study are summarised in Table 2.2. These analyses are outlined in more detail in sections 2.6.1 to 2.6.4.2 below. All linear regression modelling was done in RStudio (RStudio Team, 2015), using R (R Core Team, 2018) packages *lme4* (Bates et al., 2015) and *lmerTest* (Kuznetsova et al., 2017).

Table 2.2. Summary of all association analyses done in this study.

Written section[1]	Outcome variable	Predictor/s	Covariates	Inheritance model	Tests[2]	Adjusted α value[3]	Sample size
2.6.1	PANSS scores	Time × ROI volume	Age, gender, ancestry, baseline PANSS score, substance use	*NA*	32	1.563×10^{-3}	74
2.6.2.1	PANSS scores	Time × SNP	Age, gender, ancestry, baseline PANSS score	Genotypic	528	9.470×10^{-5}	103
				Additive	744	6.720×10^{-5}	
2.6.2.2	ROI volume	SNP	Age, gender, ancestry, substance use	Genotypic	1056	4.735×10^{-5}	74
				Additive	1488	3.360×10^{-5}	
2.6.3.1	PANSS scores	Time × CTQ scores	Age, gender, ancestry, baseline PANSS score	*NA*	24	2.083×10^{-3}	75
2.6.3.2	ROI volume	CTQ scores	Age, gender, ancestry, substance use	*NA*	48	1.042×10^{-3}	55
2.6.4.1	PANSS scores	Time × SNP × CTQ scores	Age, gender, ancestry, baseline PANSS score	Genotypic	3168	1.578×10^{-5}	75
				Additive	4464	1.120×10^{-5}	
2.6.4.2	ROI volume	SNP × CTQ scores	Age, gender, ancestry, substance use	Genotypic	6336	7.891×10^{-6}	55
				Additive	8928	5.600×10^{-6}	

PANSS = Positive and Negative Syndrome Scale; ROI = brain region of interest; SNP = single nucleotide polymorphism; CTQ = Childhood Trauma Questionnaire; Additive = Additive allelic model

[1]Corresponding written section below; [2]The number of tests performed in the model; [3]Adjusted significance threshold (α) after Bonferroni correction for multiple testing

2.7.1. Associations between baseline ROI volumes and antipsychotic treatment response

Linear mixed-effects models were used to investigate the associations between baseline volumes of the eight brain regions of interest (ROIs) and antipsychotic treatment response as determined by the change in PANSS scores over 12 months. Model diagnostics were done to assess whether the fitted models were in compliance with the assumptions for linear models, i.e. linearity, homoscedasticity, and normality, as follows: residual plots were generated for the models to visually inspect linearity and homoscedasticity; and as statistical assessments for normality are sensitive to sample size, visual methods (density and Q-Q plots) were used in combination with the Shapiro-Wilk's statistical significance test to assess normality of the residuals. Although the distribution of the residuals was satisfactory, the residual plots revealed violation of the linearity and homoscedasticity assumptions. Log-transformation of the PANSS scores improved the linearity and homoscedasticity of the residual plots, and the models were then considered suitable for the analysis. The four different log-transformed PANSS scores (positive, negative, general and total) were modelled as functions of the interaction between time of observation (PANSS assessment) and brain volumetric measures as fixed

effects, for each of the eight ROIs. A random effect was included to correct for the presence of multiple measures (PANSS scores) per individual over time. As the South African Mixed-Ancestry population is highly admixed, a panel of ancestry informative markers (AIMs) was previously developed specifically for this population group, in order to correct for differences in ancestry that may contribute to population stratification, and possibly result in spurious associations (Daya et al., 2013). All 103 patients were previously genotyped for the 96 AIMs, and for each individual, ancestral proportions were estimated in ADMIXTURE (Alexander et al., 2009) for the five base population groups (African San, African non-San, European, South and East Asian). To account for differences in ancestry, each model was adjusted for these five ancestral proportions. In addition to this, all models were adjusted for age, gender, baseline PANSS scores (log-transformed), and substance use (any substance use ever versus no substance use ever). In order to correct for multiple testing, Bonferroni correction was used, therefore the significance threshold of 0.05 was divided by the total number of tests performed. Bonferroni correction was applied separately to each family of tests as shown in Table 2.2. The number of tests was calculated as follows: (number of tests [n = 32]) = (number of ROIs [n = 8]) × (number of PANSS domains [n = 4]); resulting in an adjusted significance threshold of $\alpha = 1.563 \times 10^{-3}$ (0.05/32).

2.7.2. Genetic analyses

2.7.2.1. Associations between genetic variants and antipsychotic treatment response

Linear mixed-effects models were used to investigate associations between the prioritised genetic variants and antipsychotic treatment response. Model diagnostics were done as outlined in section 2.6.1 and PANSS scores were once again log-transformed to improve linearity and homoscedasticity. The four different log-transformed PANSS scores were modelled as functions of the interaction between time of observation and genetic factor as fixed effects. Genotypic and additive allelic models of inheritance were considered for the analyses, thus genotypes and number of minor alleles (0, 1, or 2) were the genetic predictors in the models, respectively. A random effect was included to account for the multiple measures (PANSS scores) per individual over time. All models were adjusted for age, gender, ancestry (as described in 2.6.1) and log-transformed baseline PANSS scores. For these analyses, all variants for which the cohort included less than five minor genotypes were removed due to failure of the regression models to converge. A total of 132 and 186 variants were therefore included in the genotypic and additive allelic association analyses, respectively. In order to correct for multiple testing, Bonferroni correction was applied as described in 2.6.1. For the genotypic model, the number of tests was 528, resulting in an adjusted significance threshold of $\alpha = 9.470 \times 10^{-5}$. The number of tests for the additive allelic model was 744, therefore $\alpha = 6.720 \times 10^{-5}$ (Table 2.2).

2.7.2.2. Associations between genetic variants and baseline ROI volumes

Linear models were used to investigate the associations between prioritised genetic variants and baseline ROI volumes. Model diagnostics were done as described in section 2.6.1, and all model assumptions were satisfied. Volumetric measures for the eight ROIs were modelled as functions of the respective genetic factors as fixed effects, adjusting for age, gender, substance use, and ancestry (as described in section 2.6.1). The genetic predictors in the models were genotypes for association analyses under the genotypic model, and number of minor alleles (0, 1 or 2) for association analyses under the additive allelic model of inheritance. Due

to the model errors described in section 2.6.2.1, once again 132 variants were included for analyses under the genotypic model, and 186 variants were included for the additive allelic model. Bonferroni correction was applied to account for multiple testing as described above. For the genotypic model, the number of tests was 1056, therefore $\alpha = 4.735 \times 10^{-5}$. For the additive allelic model, the number of tests was 1488 and $\alpha = 3.360 \times 10^{-5}$ (Table 2.2).

2.7.3. Childhood trauma analyses

2.7.3.1. Associations between childhood trauma and antipsychotic treatment response

Linear mixed-effects models were used to investigate the association between childhood trauma severity and antipsychotic treatment response. Model diagnostics were done as outlined in section 2.6.1 and PANSS scores were once again log-transformed to improve linearity and homoscedasticity. The four different log-transformed PANSS scores (positive, negative, general and total) were modelled as functions of the interaction between time of observation and CTQ scores as fixed effects, for each of the six CTQ scoring domains, namely emotional abuse and neglect, physical abuse and neglect, sexual abuse, and total trauma score. A random effect was included to correct for the presence of multiple measures (PANSS scores) per individual over time. All models were adjusted for age, gender, ancestry, and baseline PANSS scores (log-transformed). In order to correct for multiple testing, Bonferroni correction was used, as described above. The number of tests was 24, therefore $\alpha = 2.083 \times 10^{-3}$ (Table 2.2).

2.7.3.2. Associations between childhood trauma and baseline ROI volumes

Linear models were used to investigate the associations between childhood trauma severity and baseline ROI volumes. Model diagnostics were done as described in section 2.6.1 and all model assumptions were satisfied. Volumetric measures for the eight ROIs were modelled as functions of the six CTQ scoring domains (described in 2.6.3.1) respectively as fixed effects, adjusting for age, gender, ancestry and substance use. Bonferroni correction was used to correct for multiple testing, as described above. The number of tests was 48, therefore $\alpha = 1.042 \times 10^{-3}$ (Table 2.2).

2.7.4. Gene-environment interaction (GxE) analyses with childhood trauma

2.7.4.1. Associations between GxE and antipsychotic treatment response

To investigate the associations between GxE and antipsychotic treatment response, with childhood trauma as the environmental influence of interest, all analyses and model diagnostics were done as described in section 2.6.2.1, but CTQ scores were included as an interacting variable with the genetic predictors in the models. This was done for each of the six scoring domains for CTQ, as outlined in 2.6.3.1. Bonferroni correction was applied to account for multiple testing as described above. The number of tests for the genotypic model was 3168, therefore $\alpha = 1.578 \times 10^{-5}$. The number of tests for the additive allelic model was 4644, therefore $\alpha = 1.120 \times 10^{-5}$ (Table 2.2).

2.7.4.2. Associations between GxE and baseline ROI volumes

To investigate the associations between GxE with childhood trauma, and baseline ROI volumes, all analyses were done as described in section 2.6.2.2, but with the inclusion of CTQ scores as an interacting variable with the genetic predictors in the models. This was done for each of the six scoring domains for CTQ, as outlined in section 2.6.3.1. Bonferroni correction was used to correct for multiple testing as described above. The number of tests for the genotypic model was 6336, therefore $\alpha = 7.891 \times 10^{-6}$. For the additive allelic model, the number of tests was 8928, therefore $\alpha = 5.600 \times 10^{-6}$ (Table 2.2).

2.8. Pathway analysis

The KEGG Human database option on Enrichr (Chen et al., 2013; Kuleshov et al., 2016; https://amp.pharm.mssm.edu/Enrichr/) was used to identify pathways of interest that were enriched for genes significantly associated with antipsychotic treatment response or ROI volume in this study, either without childhood trauma interaction, or for the GxE analyses with childhood trauma.

CHAPTER 3

Results

3.1. Clinical outcomes

After 12 months of antipsychotic treatment, the patient cohort was assessed for various measures of treatment outcome, as previously reported by Chiliza et al. (2015). Considering the change in PANSS scores over time, 77 of the participants (74.8%) experienced a ≥ 25% reduction in their PANSS scores by week six, thereby achieving early response. By the end of month 12, 58 participants (56.3%) had achieved full remission according to the Remission in Schizophrenia Working Group criteria (Andreasen et al., 2005), and nine participants (8.7%) were classified as non-responders (treatment refractory).

3.2. Brain regions of interest (ROIs)

Twenty-six ROIs (volumetric measures) were identified in the literature search and are listed in Table S2. Eight of the 26 ROIs were identified in the available structural MRI data (highlighted in red and in bold in Table S2). The eight ROIs (volumetric measures) included in the study were the caudate, cortex, hippocampal tail, hippocampus, pallidum, putamen, subcortical grey matter, and total grey matter.

3.3. Candidate genes

As shown in Table S3, 134 genes linked to variation in regional brain volume were identified, 48 of which were identified through the literature search (coloured in white), and 86 of which were identified in GWAS via the NHGRI-EBI GWAS Catalog (coloured in blue). Ninety-seven genes previously associated with antipsychotic treatment response were identified, 52 from the literature search only (coloured in white), 44 from the NHGRI-EBI GWAS Catalog only (coloured in blue), and one (*ANKS1B)* identified via both the literature search and the NHGRI-EBI GWAS Catalog (coloured in purple). Fifteen genes were identified in both lists, i.e. implicated in both brain structure and antipsychotic response (coloured red and in bold), all of which were identified through the literature search only. These genes were *AKT1*, *BDNF*, *CACNA1C*, *CNR1*, *COMT*, *DISC1*, *DRD2*, *DRD3*, *DTNBP1*, *IL1RN*, *NRG1*, *OXTR*, *RGS4*, *TNFα*, and *ZNF804A*. The cannabinoid receptor 1 gene (*CNR1*) was excluded due to possible confounding effects of cannabis use in potential associations between *CNR1* variants and antipsychotic treatment response or brain structure; thus 14 genes were included as candidates for the study.

3.4. Genetic variants

From the available genome-wide genotype data, 1132 variants within the 14 candidate genes were extracted. From these variants, 192 were prioritised for inclusion in the study based on an MAF of ≥ 0.1, functional relevance, and previous implication in either brain structure or antipsychotic treatment response. The number of variants that were included for each gene is shown in Table 3.1. No variants within *AKT1* met the criteria for inclusion in the study, and so this gene was not further investigated. All prioritised variants are listed in Tables

S4 – S6, along with the reasons for inclusion and the annotations from each database or tool that was used in the prioritisation process. As shown in Table S4, 18 variants fulfilled inclusion criteria based on functional impact, as they were reported to be either missense, nonsynonymous, deleterious, damaging, probably damaging, or possibly damaging according to Ensembl (Zerbino et al., 2018) SNPnexus (SIFT and Polyphen options; Chelala et al., 2009), SIFT (Sim et al., 2012), and Polyphen-2 (Adzhubei et al., 2010). As shown in Table S5, the literature search revealed a total of 42 variants that had been previously associated with either brain structure (11 variants), antipsychotic response (21 variants), or both of these traits (10 variants). Six variants were found in the NHGRI-EBI GWAS Catalog (MacArthur et al., 2017) for association with brain structure, and none for antipsychotic treatment response. Twenty-six variants were reported to have an effect on antipsychotic efficacy, toxicity or response (including adverse drug reactions) according to the clinical and variant annotations on PharmGKB (Whirl-Carrillo et al., 2012). As shown in Table S6, 62 variants had scores ranging from '1a' to '3b' on RegulomeDB (Boyle et al., 2012). Seven variants were reported to impact miRNA binding according to PolymiRTS (Bhattacharya et al., 2014), and no variants were identified from the TarBase option on SNPnexus (not included in the table), which shows potential impact on a miRNA target site. Lastly, 94 variants were shown to affect transcription factor binding according to SNP2TFBS (Kumar et al., 2017).

Table 3.1. The number of variants per gene that were prioritised for inclusion in the study.

Gene	Prioritised variants
AKT1	0
BDNF	4
CACNA1C	39
COMT	20
DISC1	35
DRD2	15
DRD3	4
DTNBP1	4
IL1RN	4
NRG1	48
OXTR	9
RGS4	3
TNFα	2
ZNF804A	5
Total	**192**

3.5. Variant descriptive statistics

All but three of the prioritised variants were in Hardy-Weinberg equilibrium (HWE). The three variants that deviated from HWE were *CACNA1C* rs2238096 ($P = 2.661 \times 10^{-4}$), *DISC1* rs2356606 ($P = 6.761 \times 10^{-3}$), and *NRG1* rs1623372 ($P = 7.085 \times 10^{-3}$). These variants were included in downstream analyses. Cases of LD between significant variants are mentioned in following sections, and the corresponding LD plots for these variants are shown in Tables S7a - e.

3.6. Association analyses

In all of the following sections, results are reported as significant if associations surpassed a Bonferroni corrected significance threshold. In cases where no significant associations were identified, an uncorrected significance threshold of $\alpha = 0.05$ was considered for the observation of trends.

3.6.1. Associations between baseline ROI volumes and antipsychotic treatment response

No significant associations were identified between the eight brain regions of interest (volumetric measures) and the four PANSS domains (positive, negative, general and total scores), after Bonferroni correction for multiple testing ($\alpha = 1.563 \times 10^{-3}$). No trends were observed when considering an uncorrected significance threshold ($\alpha = 0.05$). Results are not shown.

3.6.2. Genetic analyses

3.6.2.1. Associations between genetic variants and antipsychotic treatment response

Ten variants in *CACNA1C*, *NRG1*, and *OXTR* were significantly associated with antipsychotic treatment response as determined by the change in log-transformed PANSS scores over 12 months (Table 3.2). Two of these variants (*NRG1* rs1481728 and rs7005124) were significantly associated with treatment response under the genotypic model of inheritance only ($P < 9.470 \times 10^{-5}$), four of the variants (*CACNA1C* rs215976, *NRG1* rs16879304 and rs2439312, and *OXTR* rs4686301) under the additive allelic model of inheritance only ($P < 6.720 \times 10^{-5}$), and the remaining four variants (*CACNA1C* rs10161032, *NRG1* rs6987996 and rs17645417, and *OXTR* rs237884) were significantly associated with treatment response for both the genotypic and additive allelic inheritance models ($P < 9.470 \times 10^{-5}$, and $P < 6.720 \times 10^{-5}$, respectively).

Eleven significant associations (involving five different variants) showed poorer response to antipsychotic treatment for either negative, general, or total symptoms, as per the positive values of the effect estimates (relative increase in log-transformed PANSS scores). These associations were for *CACNA1C* rs10161032, *OXTR* rs4686301, and *NRG1* rs6987996, rs17645417, and rs16879304. Six associations were for improved response to treatment as per the negative effect estimate values (relative decrease in log-transformed PANSS scores). Variants associated with improved treatment response (for negative symptoms) were *CACNA1C* rs215976, *OXTR* rs237884, and *NRG1* rs1481728, rs7005124, and rs2439312. The most significant result was the association between *NRG1* rs17645417 and poorer treatment response for negative symptoms with each additional *C* allele ($P = 5.25 \times 10^{-7}$). Two of the variants in *NRG1* (rs17645417 and rs2439312) were in LD, the plot for which is shown in Table S7a. The specific genotypes, alleles, and PANSS scoring domains involved in the associations are displayed in Table 3.2, along with the estimated effect sizes, 95% confidence intervals, and *P* values for each association.

Table 3.2. Genetic variants significantly associated with antipsychotic treatment response (ATR) as defined by the change in log-transformed PANSS scores over 12 months, considering the genotypic and additive allelic models of inheritance.

Genotypic model of inheritance ($\alpha = 9.470 \times 10^{-5}$)							
Gene	**SNP**	**PANSS domain**	**Contrast**	**ATR[a]**	**Effect estimate**	**95% CI**	***P* value**
CACNA1C	**rs10161032**	General	*CC* vs *TT*	✗	6.12×10^{-3}	3.14×10^{-3} to 9.10×10^{-3}	6.14×10^{-5}
	rs10161032	Negative	*CC* vs *TT*	✗	6.30×10^{-3}	3.26×10^{-3} to 9.35×10^{-3}	5.40×10^{-5}
NRG1	**rs6987996**	Negative	*TT* vs *CC*	✗	5.49×10^{-3}	3.18×10^{-3} to 7.80×10^{-3}	3.69×10^{-6}
	rs1481728	Negative	*TT* vs *GG*	✓	-7.81×10^{-3}	-1.15×10^{-2} to -4.10×10^{-3}	4.00×10^{-5}
	rs7005124	Negative	*GT* vs *TT*	✓	-4.43×10^{-3}	-6.35×10^{-3} to -2.50×10^{-3}	7.59×10^{-6}
	rs17645417	Negative	*CT* vs *TT*	✗	4.49×10^{-3}	2.49×10^{-3} to 6.49×10^{-3}	1.16×10^{-5}
	rs17645417	Negative	*CC* vs *TT*	✗	6.53×10^{-3}	3.68×10^{-3} to 9.38×10^{-3}	8.13×10^{-6}
OXTR	**rs237884**	Negative	*GG* vs *AA*	✓	-5.03×10^{-3}	-7.42×10^{-3} to -2.64×10^{-3}	4.15×10^{-5}
Additive allelic model of inheritance ($\alpha = 6.720 \times 10^{-5}$)							
Gene	**SNP**	**PANSS domain**	**Contrast**	**ATR[a]**	**Effect estimate**	**95% CI**	***P* value**
CACNA1C	**rs10161032**	General	each *C*	✗	2.78×10^{-3}	1.43×10^{-3} to 4.14×10^{-3}	6.00×10^{-5}
	rs215976	Negative	each *T*	✓	-4.13×10^{-3}	-6.05×10^{-3} to -2.18×10^{-3}	3.42×10^{-5}
NRG1	**rs6987996**	Negative	each *T*	✗	2.83×10^{-3}	1.69×10^{-3} to 3.97×10^{-3}	1.48×10^{-6}
	rs16879304	Negative	each *C*	✗	4.43×10^{-3}	2.54×10^{-3} to 6.32×10^{-3}	5.02×10^{-6}
	rs17645417	Negative	each *C*	✗	3.53×10^{-3}	2.16×10^{-3} to 4.90×10^{-3}	5.25×10^{-7}
	rs17645417	Total	each *C*	✗	2.68×10^{-3}	1.39×10^{-3} to 3.96×10^{-3}	4.91×10^{-5}
	rs2439312	Negative	each *T*	✓	-3.50×10^{-3}	-5.14×10^{-3} to -1.86×10^{-3}	3.14×10^{-5}
OXTR	**rs237884**	Negative	each *G*	✓	-2.58×10^{-3}	-3.76×10^{-3} to -1.39×10^{-3}	2.46×10^{-5}
	rs4686301	Negative	each *T*	✗	3.64×10^{-3}	2.17×10^{-3} to 5.11×10^{-3}	1.42×10^{-6}

PANSS domain = Positive and Negative Syndrome Scale scoring domain (positive, negative, general, or total); ATR = Antipsychotic treatment response; Effect estimate = Difference in log-transformed PANSS scores between the different genotypes/ with each additional minor allele, multiplied by time; 95% CI = 95% confidence interval; *P* value = unadjusted *P* value.

[a]Indicates relative response to treatment over time between genotypes (genotypic model) or with each additional minor allele (additive model); ✗ = worse treatment trajectory; ✓ = improved treatment trajectory. Variants in bold typeset were significant under both the genotypic and additive inheritance models. Variants highlighted in yellow are in LD with another yellow variant within that gene.

3.6.2.2. Associations between genetic variants and baseline ROI volumes

No variants were significantly associated with any of the eight ROI volumes. An uncorrected significance threshold ($\alpha = 0.05$) was therefore considered in order to observe imaging genetics trends of interest with respect to antipsychotic treatment response. Three of the variants that were significantly associated with antipsychotic treatment response in this study (Table 3.2), showed tentative trends of interest ($P < 0.05$) for ROI volumes, and are shown in Table 3.3, along with the ROIs, estimated effect sizes, 95% confidence intervals, *P* values, and associated treatment outcomes which were taken from Table 3.2.

CACNA1C rs10161032, that was significantly associated with poorer response to treatment (Table 3.2), showed trend-level increases in caudate and subcortical grey matter volumes under both the genotypic and additive inheritance models (Table 3.3). *OXTR* rs237884, that was significantly associated with improved treatment response, showed trend-level reductions in putamen volumes under both inheritance models. Lastly, *NRG1* rs2439312, that was significantly associated with improved treatment response, showed trend-level increases in cortex and total grey matter volumes under the additive model of inheritance.

Table 3.3. Genetic variants of interest for ROI volumes (uncorrected *P* < 0.05), that were significantly associated with antipsychotic response (Table 3.2).

Genotypic model of inheritance								
Gene	**SNP**	**Contrast**	**ATR[a]**	**Brain ROI**	**Volume[b]**	**Effect estimate[c]**	**95% CI[c]**	***P* value[c]**
CACNA1C	**rs10161032**	*CC* vs *TT*	✗	Caudate	↑	6.79×10^{-2}	1.48×10^{-2} to 0.12	0.0130
				Subcortical grey matter	↑	0.29	6.49×10^{-3} to 0.57	0.0451
OXTR	**rs237884**	*GG* vs *AA*	✓	Putamen	↓	-5.64×10^{-2}	-0.11 to -4.25×10^{-3}	0.0345
Additive allelic model of inheritance								
Gene	**SNP**	**Contrast**	**ATR[a]**	**Brain ROI**	**Volume[b]**	**Effect estimate[c]**	**95% CI[c]**	***P* value[c]**
CACNA1C	**rs10161032**	each *C*	✗	Caudate	↑	3.34×10^{-2}	1.02×10^{-2} to 5.65×10^{-2}	0.0054
				Subcortical grey matter	↑	0.13	8.29×10^{-3} to 0.25	0.0367
NRG1	rs2439312	each *T*	✓	Cortex	↑	1.51	0.25 to 2.77	0.0194
				Total grey matter	↑	1.76	0.22 to 3.29	0.0253
OXTR	**rs237884**	each *G*	✓	Putamen	↓	-2.99×10^{-2}	-5.53×10^{-2} to -4.39×10^{-3}	0.0223

ATR = Antipsychotic treatment response; Brain ROI = Brain region of interest; Effect estimate = Percentage increase or reduction in ROI volume between different genotypes/ with each additional minor allele; 95% CI = 95% confidence interval; *P* value = unadjusted *P* value. [a]Indicates relative response to treatment over time between genotypes (genotypic model) or with each additional minor allele (additive model); ✗ = worse treatment trajectory; ✓ = improved treatment trajectory (taken from Table 3.2). [b]Indicates the overall difference in brain volume (↓ = smaller volume; ↑ = larger volume). [c]Indicates association statistics from Brain ROI analyses.
Variants in bold typeset occur under both the genotypic and additive inheritance models.

3.6.3. Childhood trauma analyses

3.6.3.1. Associations between childhood trauma and antipsychotic treatment response

No significant associations were identified between the six childhood trauma domains (emotional abuse and neglect, physical abuse and neglect, sexual abuse, and total trauma scores) and the four PANSS domains (positive, negative, general and total scores). However, when considering an uncorrected significance threshold ($\alpha = 0.05$), a trend was observed between the severity of emotional neglect and the change in log-transformed PANSS positive scores over time ($P = 0.010$). This trend suggests that increased severity of emotional neglect may result in a poorer treatment trajectory in the positive symptom domain (effect estimate = 2.991×10^{-4}; 95% CI = 7.166×10^{-5} to 5.269×10^{-4}). Other results are not shown.

3.6.3.2. Associations between childhood trauma and baseline ROI volumes

No significant associations were identified between the six childhood trauma domains and the eight brain regions of interest (volumetric measures), and no trends of interest were observed when considering an uncorrected threshold ($\alpha = 0.05$). Results are not shown.

3.6.4. Gene-environment interaction (GxE) analyses with childhood trauma

3.6.4.1. Associations between GxE and antipsychotic treatment response

Thirty-one unique GxE (between 27 different variants and varying childhood trauma scores), were significantly associated with antipsychotic treatment response under the genotypic model of inheritance. The specific associations are listed in Table 3.4, showing the variants and genotypes involved, the categories of childhood trauma with which the variants interacted, the PANSS scoring domains affected, along with the estimated effect sizes, 95% confidence intervals and unadjusted *P* values. The 27 variants highlighted in these analyses were within *CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR*. These variants were found to influence treatment trajectory based on the interaction between childhood trauma severity and specific genotypes. One of these variants (*CACNA1C* rs2238096) deviated from Hardy-Weinberg equilibrium. All of the variants in *COMT*, *DRD3*, and *OXTR* were found to be in LD with at least one other significant variant within the same gene (highlighted in yellow in Table 3.4), and the LD plots for these are displayed in Tables S7b – d. Sixteen associations were for improved treatment response, and fifteen associations were for poorer treatment response. Significantly influenced treatment response outcomes were evident for negative, general, and total symptoms, but not for positive symptoms. Each of the six childhood trauma scoring domains were involved in the significant GxE.

Considering the additive model of inheritance, 34 unique GxE between 18 different variants and varying childhood trauma scores, were significantly associated with antipsychotic treatment response (Table 3.5). These variants were found to influence treatment trajectory based on the interaction between childhood trauma severity and the number of minor alleles present. The 18 significant variants were within *CACNA1C*, *COMT*, *DISC1*, *DRD3*, and *NRG1*, and are shown in Table 3.5, with the categories of childhood trauma involved, the

PANSS scoring domains affected, the estimated effect sizes, 95% confidence intervals and unadjusted *P* values. Eleven of these variants were also significant under the genotypic model of inheritance (Table 3.4). All of the variants in *DRD3* were in LD with another *DRD3* variant (highlighted in yellow in Table 3.5), and the LD plot for *DRD3* is shown in Table S7c. All but one of the variants in *DISC1*, and all but two of the variants in *NRG1*, were in LD with at least one other significant variant within the same gene (LD plots displayed in Table S7e, and Table S7a, respectively), and are highlighted in yellow in Table 3.5. Fifteen associations were for improved treatment response, and 19 associations were for poorer treatment response. As observed for the genotypic model, these associations involved either negative, general, or total symptoms, but not positive symptoms, and each of the six childhood trauma scoring domains were involved in the significant associations.

3.6.4.2. Associations between GxE and baseline ROI volumes

No variants were significantly associated with any of the eight ROI volumes, when interacting with childhood trauma. In order to observe exploratory trends of interest for imaging gene-environment interactions (iGxE) of antipsychotic treatment response, an uncorrected significance threshold ($\alpha = 0.05$) was considered. Ten of the GxE that were significantly associated with antipsychotic treatment response in this study (Tables 3.4 and 3.5), showed tentative trends of interest ($P < 0.05$) for ROI volumes. These 10 GxE are displayed in Table 3.6, along with the childhood trauma domain involved, specific ROIs, estimated effect sizes, 95% confidence intervals, *P* values, and associated treatment outcomes that were taken from Tables 3.4 and 3.5. All of the variants in *DISC1* and *NRG1*, were in LD with at least one other significant variant within the same gene (LD plots displayed in Table S7e, and Table S7a, respectively), and are highlighted in yellow in Table 3.6. Six GxE with childhood trauma that were significantly associated with poorer response to antipsychotic treatment, showed trend-level reductions in several ROIs (caudate, cortex, pallidum, putamen, subcortical grey matter, and total grey matter). Conversely, five GxE that were significantly associated with improved response to antipsychotic treatment showed trend-level increases in putamen and hippocampal volumes.

Table 3.4. Genetic variants significantly associated with antipsychotic treatment response when interacting with childhood trauma, under the genotypic model of inheritance ($P < 1.578 \times 10^{-5}$).

Gene	SNP	CTQ domain	PANSS domain	Contrast	Response[a]	Effect estimate	95% CI	*P* value
CACNA1C	rs2238096	EN	Negative	*CC* vs *AA*	×	1.51×10^{-3}	8.25×10^{-4} to 2.20×10^{-3}	1.84×10^{-5}
	rs2429127	EN	General	*CT* vs *TT*	✓	-7.92×10^{-4}	-1.15×10^{-3} to -4.40×10^{-4}	1.23×10^{-5}
	rs4126711	SA	Negative	*TC* vs *CC*	×	1.17×10^{-3}	7.385×10^{-4} to 1.59×10^{-3}	1.22×10^{-7}
	rs4765687	PN	Negative	*AG* vs *GG*	✓	-1.50×10^{-3}	-2.14×10^{-3} to -8.65×10^{-4}	4.79×10^{-6}
COMT	rs2020917	SA	Negative	*TC* vs *CC*	×	1.44×10^{-3}	8.51×10^{-4} to 2.02×10^{-3}	1.81×10^{-6}
	rs2075507	PN	Negative	*AG* vs *GG*	✓	-1.55×10^{-3}	-2.13×10^{-3} to -9.65×10^{-4}	2.62×10^{-7}
	rs2239393	SA	Negative	*GA* vs *AA*	×	1.32×10^{-3}	7.61×10^{-4} to 1.88×10^{-3}	4.67×10^{-6}
	rs4818	SA	Negative	*CG* vs *GG*	×	1.14×10^{-3}	6.47×10^{-4} to 1.64×10^{-3}	7.77×10^{-6}
	rs737865	SA	Negative	*CT* vs *TT*	×	1.50×10^{-3}	9.91×10^{-4} to 2.01×10^{-3}	1.33×10^{-8}
	rs737866	SA	Negative	*GA* vs *AA*	×	1.50×10^{-3}	9.91×10^{-4} to 2.01×10^{-3}	1.33×10^{-8}
	rs933271	SA	General	*CT* vs *TT*	×	9.87×10^{-4}	5.40×10^{-4} to 1.43×10^{-3}	1.73×10^{-5}
DISC1	**rs12757857**	PA	Negative	*TC* vs *CC*	✓	-9.83×10^{-4}	-1.40×10^{-3} to -5.64×10^{-4}	5.07×10^{-6}
	rs2487453	SA	Negative	*GA* vs *AA*	✓	-1.19×10^{-3}	-1.69×10^{-3} to -6.83×10^{-4}	4.93×10^{-6}
	rs701160	SA	Negative	*AA* vs *GG*	✓	-1.57×10^{-3}	-2.15×10^{-3} to -9.88×10^{-4}	1.66×10^{-7}
DRD3	**rs1394016**	EA	General	*GG* vs *AA*	×	1.85×10^{-3}	1.01×10^{-3} to 2.69×10^{-3}	1.70×10^{-5}
	rs1394016	SA	Negative	*GA* vs *AA*	×	1.53×10^{-3}	1.00×10^{-3} to 2.06×10^{-3}	2.46×10^{-8}
	rs167771	SA	General	*AA* vs *GG*	×	2.68×10^{-3}	1.55×10^{-3} to 3.80×10^{-3}	3.93×10^{-6}
	rs6280	SA	Negative	*TC* vs *CC*	×	1.10×10^{-3}	6.82×10^{-4} to 1.52×10^{-3}	3.53×10^{-7}
	rs9825563	SA	General	*GG* vs *AA*	✓	-1.67×10^{-3}	-2.35×10^{-3} to -9.90×10^{-4}	1.89×10^{-6}
	rs9825563	SA	Negative	*GG* vs *AA*	✓	-1.94×10^{-3}	-2.63×10^{-3} to -1.25×10^{-3}	5.56×10^{-8}
	rs9825563	SA	Total	*GG* vs *AA*	✓	-1.56×10^{-3}	-2.21×10^{-3} to -9.04×10^{-4}	3.68×10^{-6}
NRG1	rs2919392	EN	Negative	*CC* vs *TT*	×	1.63×10^{-3}	8.94×10^{-4} to 2.36×10^{-3}	1.56×10^{-5}
	rs10503901	SA	Negative	*TT* vs *CC*	✓	-1.23×10^{-3}	-1.77×10^{-3} to -6.91×10^{-4}	8.87×10^{-6}
	rs3847131	SA	Negative	*TC* vs *CC*	✓	-1.04×10^{-3}	-1.48×10^{-3} to -5.89×10^{-4}	6.77×10^{-6}
	rs3924999	PN	Negative	*AA* vs *GG*	✓	-1.87×10^{-3}	-2.69×10^{-3} to -1.05×10^{-3}	8.89×10^{-6}
	rs6987996	PN	Negative	*TT* vs *CC*	✓	-1.74×10^{-3}	-2.51×10^{-3} to -9.66×10^{-4}	1.19×10^{-5}
	rs6987996	Total	Negative	*TT* vs *CC*	✓	-3.96×10^{-4}	-5.62×10^{-4} to -2.31×10^{-4}	3.14×10^{-6}
	rs796549	EN	Negative	*AG* vs *GG*	×	1.13×10^{-3}	7.21×10^{-4} to 1.53×10^{-3}	7.76×10^{-8}
OXTR	rs11706648	SA	Negative	*CA* vs *AA*	✓	-9.95×10^{-4}	-1.44×10^{-3} to -5.52×10^{-4}	1.23×10^{-5}
	rs237885	SA	Negative	*TG* vs *GG*	✓	-1.00×10^{-3}	-1.44×10^{-3} to -5.60×10^{-4}	1.05×10^{-5}
	rs237888	SA	Negative	*CC* vs *TT*	×	2.00×10^{-3}	1.26×10^{-3} to 2.73×10^{-3}	1.49×10^{-7}

CTQ domain = Childhood Trauma Questionnaire scoring domain (EN = emotional neglect, EA = emotional abuse, PN = physical neglect, PA = physical abuse, SA = sexual abuse, Total = overall trauma score); PANSS domain = Positive and Negative Syndrome Scale scoring domain (positive, negative, general, or total scores); Effect estimate = Difference in log-transformed PANSS scores between the different genotypes, multiplied by time and CTQ score; 95% CI = 95% confidence interval; *P* value = unadjusted *P* value.

[a]Indicates relative response to treatment over time between genotypes (× = worse treatment trajectory; ✓ = improved treatment trajectory).

Variants in bold typeset were significant under both the genotypic and additive inheritance models. Variants in red font deviate from HWE. Variants highlighted in yellow are in LD with another yellow variant within that gene.

Table 3.5. Genetic variants significantly associated with antipsychotic treatment response when interacting with childhood trauma, under the additive allelic model of inheritance ($P < 1.120 \times 10^{-5}$).

Gene	SNP	CTQ domain	PANSS domain	Contrast	Response[a]	Effect estimate	95% CI	*P* value
CACNA1C	rs2239084	SA	General	each *A*	×	1.83×10^{-3}	1.16×10^{-3} to 2.50×10^{-3}	1.36×10^{-7}
	rs2239084	SA	Total	each *A*	×	1.68×10^{-3}	1.03×10^{-3} to 2.33×10^{-3}	4.57×10^{-7}
	rs4126711	SA	Negative	each *T*	×	8.98×10^{-4}	5.70×10^{-4} to 1.23×10^{-3}	1.16×10^{-7}
COMT	**rs2075507**	PN	Negative	each *G*	✓	-1.28×10^{-3}	-1.79×10^{-3} to -7.63×10^{-4}	1.51×10^{-6}
DISC1	**rs12757857**	PA	Negative	each *T*	✓	-6.36×10^{-4}	-9.01×10^{-4} to -3.72×10^{-4}	2.97×10^{-6}
	rs1407601	EN	Negative	each *C*	×	1.25×10^{-3}	8.72×10^{-4} to 1.63×10^{-3}	2.44×10^{-10}
	rs1407601	PN	Negative	each *C*	×	1.64×10^{-3}	1.07×10^{-3} to 2.20×10^{-3}	2.07×10^{-8}
	rs701160	SA	Negative	each *A*	✓	-7.34×10^{-4}	-1.02×10^{-3} to -4.48×10^{-4}	6.36×10^{-7}
	rs7552697	Total	Negative	each *C*	×	2.65×10^{-4}	1.49×10^{-4} to 3.80×10^{-4}	8.96×10^{-6}
DRD3	**rs1394016**	SA	General	each *G*	×	1.25×10^{-3}	7.63×10^{-4} to 1.73×10^{-3}	5.99×10^{-7}
	rs1394016	SA	Negative	each *G*	×	1.44×10^{-3}	9.46×10^{-4} to 1.94×10^{-3}	2.03×10^{-8}
	rs1394016	SA	Total	each *G*	×	1.20×10^{-3}	7.40×10^{-4} to 1.67×10^{-3}	4.96×10^{-7}
	rs167771	SA	General	each *A*	×	9.21×10^{-4}	5.32×10^{-4} to 1.31×10^{-3}	4.32×10^{-6}
	rs167771	SA	Negative	each *A*	×	9.96×10^{-4}	5.96×10^{-4} to 1.40×10^{-3}	1.38×10^{-6}
	rs167771	SA	Total	each *A*	×	8.61×10^{-4}	4.88×10^{-4} to 1.23×10^{-3}	7.14×10^{-6}
	rs6280	SA	General	each *T*	×	9.23×10^{-4}	5.63×10^{-4} to 1.28×10^{-3}	6.47×10^{-7}
	rs6280	SA	Negative	each *T*	×	9.30×10^{-4}	5.56×10^{-4} to 1.30×10^{-3}	1.36×10^{-6}
	rs6280	SA	Total	each *T*	×	8.03×10^{-4}	4.57×10^{-4} to 1.15×10^{-3}	6.59×10^{-6}
	rs9825563	SA	General	each *G*	✓	-8.51×10^{-4}	-1.15×10^{-3} to -5.55×10^{-4}	2.65×10^{-8}
	rs9825563	SA	Negative	each *G*	✓	-1.04×10^{-3}	-1.34×10^{-3} to -7.38×10^{-4}	3.84×10^{-11}
	rs9825563	SA	Total	each *G*	✓	-8.01×10^{-4}	-1.09×10^{-3} to -5.17×10^{-4}	5.04×10^{-8}
NRG1	**rs10503901**	SA	Negative	each *T*	✓	-6.16×10^{-4}	-8.85×10^{-4} to -3.46×10^{-4}	8.81×10^{-6}
	rs11778887	EA	Negative	each *G*	✓	-7.57×10^{-4}	-1.05×10^{-3} to -4.64×10^{-4}	5.32×10^{-7}
	rs11778887	EN	Negative	each *G*	✓	-6.76×10^{-4}	-9.65×10^{-4} to -3.87×10^{-4}	5.54×10^{-6}
	rs11778887	PN	Negative	each *G*	✓	-1.04×10^{-3}	-1.50×10^{-3} to -5.92×10^{-4}	7.34×10^{-6}
	rs11778887	Total	Negative	each *G*	✓	-2.46×10^{-4}	-3.34×10^{-4} to -1.58×10^{-4}	6.93×10^{-8}
	rs16879067	EA	Negative	each *T*	✓	-7.56×10^{-4}	-1.06×10^{-3} to -4.55×10^{-4}	1.05×10^{-6}
	rs16879067	Total	Negative	each *T*	✓	-2.44×10^{-4}	-3.34×10^{-4} to -1.54×10^{-4}	1.63×10^{-7}
	rs2466049	EN	Negative	each *T*	×	1.00×10^{-3}	5.65×10^{-4} to 1.44×10^{-3}	8.09×10^{-6}
	rs2466049	PN	Negative	each *T*	×	1.85×10^{-3}	1.09×10^{-3} to 2.60×10^{-3}	2.20×10^{-6}
	rs3847131	EN	General	each *T*	×	5.65×10^{-4}	3.21×10^{-4} to 8.09×10^{-4}	6.57×10^{-6}
	rs3847131	EN	Total	each *T*	×	5.23×10^{-4}	2.90×10^{-4} to 7.56×10^{-4}	1.27×10^{-5}
	rs3924999	PN	Negative	each *A*	✓	-1.07×10^{-3}	-1.45×10^{-3} to -6.76×10^{-4}	1.14×10^{-7}
	rs4733094	PN	Negative	each *A*	✓	-1.06×10^{-3}	-1.52×10^{-3} to -6.03×10^{-4}	7.29×10^{-6}

CTQ domain = Childhood Trauma Questionnaire scoring domain (EN = emotional neglect, EA = emotional abuse, PN = physical neglect, PA = physical abuse, SA = sexual abuse, Total = overall trauma score); PANSS domain = Positive and Negative Syndrome Scale scoring domain (positive, negative, general, or total scores); Effect estimate = Difference in log-transformed PANSS scores with each additional minor allele, multiplied by time and CTQ score; 95% CI = 95% confidence interval; *P* value = unadjusted *P* value.

[a]Indicates relative response to treatment over time with each additional minor allele (× = worse treatment trajectory; ✓ = improved treatment trajectory).

Variants in bold typeset were significant under both the genotypic and additive inheritance models. Variants highlighted in yellow are in LD with another yellow variant within that gene.

Table 3.6. Genetic variants of interest for ROI volumes ($P < 0.05$), that were significantly associated with antipsychotic response (Tables 3.4 and 3.5) when interacting with childhood trauma.

Genotypic model of inheritance									
Gene	**SNP**	**CTQ domain**	**Contrast**	**ATR[a]**	**Brain ROI**	**Volume[b]**	**Effect estimate[c]**	**95% CI[c]**	***P* value[c]**
CACNA1C	**rs4126711**	SA	*TC* vs *CC*	✗	Putamen	↓	-1.05×10^{-2}	-1.91×10^{-2} to -1.87×10^{-3}	0.0183
DISC1	rs701160	SA	*AA* vs *GG*	✓	Putamen	↑	1.08×10^{-2}	6.23×10^{-5} to 2.16×10^{-2}	0.0487
NRG1	rs796549	EN	*AG* vs *GG*	✗	Cortex	↓	-0.39	-0.74 to -0.05	0.0265
					Total grey matter	↓	-0.42	-0.83 to -1.18×10^{-2}	0.0441
Additive allelic model of inheritance									
Gene	**SNP**	**CTQ domain**	**Contrast**	**ATR[a]**	**Brain ROI**	**Volume[b]**	**Effect estimate[c]**	**95% CI[c]**	***P* value[c]**
CACNA1C	**rs4126711**	SA	each *T*	✗	Pallidum	↓	-2.79×10^{-3}	-5.39×10^{-3} to -1.98×10^{-4}	0.0355
					Putamen	↓	-9.15×10^{-3}	-1.56×10^{-2} to -2.71×10^{-3}	0.0065
DISC1	rs1407601	EN	each *C*	✗	Pallidum	↓	-3.44×10^{-3}	-6.63×10^{-3} to -2.42×10^{-4}	0.0357
					Putamen	↓	-1.05×10^{-2}	-1.86×10^{-2} to -2.36×10^{-3}	0.0127
	rs12757857	PA	each *T*	✓	Hippocampus	↑	4.02×10^{-3}	6.89×10^{-4} to 7.36×10^{-3}	0.0191
	rs7552697	Total	each *C*	✗	Subcortical grey matter	↓	-1.01×10^{-2}	-2.00×10^{-2} to -1.88×10^{-4}	0.0460
NRG1	rs11778887	EN	each *G*	✓	Hippocampus	↑	4.39×10^{-3}	6.54×10^{-4} to 8.13×10^{-3}	0.0223
	rs11778887	PN	each *G*	✓	Hippocampus	↑	6.93×10^{-3}	8.32×10^{-4} to 1.30×10^{-2}	0.0268
	rs2466049	PN	each *T*	✗	Caudate	↓	-1.37×10^{-2}	-2.65×10^{-2} to -9.64×10^{-4}	0.0357
	rs4733094	PN	each *A*	✓	Hippocampus	↑	6.65×10^{-3}	1.47×10^{-4} to 1.31×10^{-2}	0.0452

CTQ domain = Childhood Trauma Questionnaire scoring domain (EN = emotional neglect, EA = emotional abuse, PN = physical neglect, PA = physical abuse, SA = sexual abuse, Total = overall trauma score); ATR = Antipsychotic treatment response; Brain ROI = Brain region of interest; Effect estimate = Percentage increase or reduction in ROI volume between different genotypes/ with each additional minor allele, multiplied by CTQ score; 95% CI = 95% confidence interval; *P* value = unadjusted *P* value.

[a]Indicates relative response to treatment over time between genotypes (genotypic model) or with each additional minor allele (additive model); ✗ = worse treatment trajectory; ✓ = improved treatment trajectory (taken from Tables 3.4 and 3.5). [b]Indicates the overall difference in brain volume (↓ = smaller volume; ↑ = larger volume). [c]Indicates association statistics from Brain ROI analyses.

Variants in bold typeset were significant under both the genotypic and additive inheritance models. Variants highlighted in yellow are in LD with another yellow variant within that gene.

3.7. Pathway analysis

No variants were significantly associated with ROI volumes in the genetic analyses nor in the GxE analyses. Enrichment analysis was therefore done for all of the genes that were significantly associated with antipsychotic treatment response in this study, with and without childhood trauma interaction, i.e. *CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR*. A total of 33 pathways were identified involving *CACNA1C*, *COMT*, *DRD3*, *NRG1*, and *OXTR*, shown in Table 3.7. Five of these pathways involved more than one gene of interest, and were the top five most significant pathways (ordered by *P* value). These were the "Dopaminergic synapse" (involving *CACNA1C*, *COMT*, *DRD3*), "Oxytocin signalling pathway" (*OXTR* and *CACNA1C*), "Calcium signalling pathway" (*OXTR* and *CACNA1C*), "cAMP signalling pathway" (*OXTR* and *CACNA1C*), and "Neuroactive ligand-receptor interaction" (*OXTR* and *DRD3*). *CACNA1C* was involved in 29 of the pathways.

Table 3.7. Enrichr output showing KEGG Human pathways involving genes significantly associated with antipsychotic treatment response in this study (with and without childhood trauma interaction).

KEGG 2019 Human Pathway[a]	Genes[b]	*P* value[c]
Dopaminergic synapse	*CACNA1C*, *COMT*, *DRD3*	5.41×10^{-6}
Oxytocin signalling pathway	*OXTR*, *CACNA1C*	8.55×10^{-4}
Calcium signalling pathway	*OXTR*, *CACNA1C*	0.001
cAMP signalling pathway	*OXTR*, *CACNA1C*	0.002
Neuroactive ligand-receptor interaction	*OXTR*, *DRD3*	0.004
Tyrosine metabolism	*COMT*	0.011
Type II diabetes mellitus	*CACNA1C*	0.014
Steroid hormone biosynthesis	*COMT*	0.018
Cortisol synthesis and secretion	*CACNA1C*	0.019
Long-term potentiation	*CACNA1C*	0.020
Amphetamine addiction	*CACNA1C*	0.020
Renin secretion	*CACNA1C*	0.021
Arrhythmogenic right ventricular cardiomyopathy	*CACNA1C*	0.021
Cardiac muscle contraction	*CACNA1C*	0.023
Taste transduction	*CACNA1C*	0.025
Hypertrophic cardiomyopathy	*CACNA1C*	0.025
ErbB signalling pathway	*NRG1*	0.025
Insulin secretion	*CACNA1C*	0.026
GABAergic synapse	*CACNA1C*	0.026
Dilated cardiomyopathy	*CACNA1C*	0.027
GnRH signalling pathway	*CACNA1C*	0.028
Circadian entrainment	*CACNA1C*	0.029
Aldosterone synthesis and secretion	*CACNA1C*	0.029
Cholinergic synapse	*CACNA1C*	0.033
Serotonergic synapse	*CACNA1C*	0.033
Glutamatergic synapse	*CACNA1C*	0.034
Vascular smooth muscle contraction	*CACNA1C*	0.039
Adrenergic signalling in cardiomyocytes	*CACNA1C*	0.043
Retrograde endocannabinoid signalling	*CACNA1C*	0.044
Cushing syndrome	*CACNA1C*	0.046
cGMP-PKG signalling pathway	*CACNA1C*	0.049
Alzheimer disease	*CACNA1C*	0.050
MAPK signalling pathway	*CACNA1C*	0.085

[a]Pathway according to the KEGG 2019 Human database. [b]Genes from input list involved in pathway. [c]From Enrichr output, computed from the Fisher exact test, which is a proportion test that assumes a binomial distribution and independence for probability of any gene belonging to any set.

CHAPTER 4

Discussion

This study made use of an integrative research approach to explore the interplay between genetics, brain structure, and childhood trauma, in the context of differential antipsychotic treatment outcomes in schizophrenia. This was done by conducting a number of different association analyses, in an attempt to reveal trends that may contribute to the understanding of various underlying mechanisms involved in antipsychotic treatment response.

4.1. Candidate genes and variants

To our knowledge, aside from the current study, there have been no studies investigating imaging genetics in antipsychotic treatment response considering structural neuroimaging measurements. The candidate genes included in this study, based on previous implication in both brain structure and antipsychotic treatment response, were therefore selected if they were identified in 1) genetic studies of brain structure, and 2) genetic studies of antipsychotic response, respectively. Fourteen genes were identified in the two lists, which provides evidence for a genetic overlap between the two traits (brain structure and treatment response). This is further supported when considering specific variants identified in these studies. Ten of the variants prioritised for this study were found to influence both brain structure and antipsychotic treatment response in previous studies (Table S5). These were: *BDNF* rs6265 (Ho et al., 2006; Zhang et al., 2013), *CACNA1C* rs1006737 (Porcelli et al., 2015; Wang et al., 2011), *COMT* rs4680 (Gupta et al., 2009; Ohnishi et al., 2005), *DISC1* rs6675281 (Mouaffak et al., 2011; Trost et al., 2013), *DRD2* rs1800497 (Li et al., 2018; Zhang et al., 2010), *DRD3* rs6280 (Takahashi et al., 2008; Vehof et al., 2012), *NRG1* rs35753505 (Mostaid et al., 2017; Suárez-Pinilla et al., 2015), *RGS4* rs2661319 (Lane et al., 2008; Prasad et al., 2005), *TNFα* rs1800629 (Baune et al., 2012; Zai et al., 2006), and *ZNF804A* rs1344706 (Mössner et al., 2012; Wassink et al., 2012). These findings warrant further investigation of the genetic overlap between brain structure and antipsychotic response. Although very few fMRI imaging genetics studies of antipsychotic treatment response have been performed, one of these studies found that the interaction between *DRD2* rs1076560 and *AKT1* rs1030233 was associated with differing cingulate response and reduced behavioural accuracy during attentional processing in healthy individuals, and with improved antipsychotic treatment response in schizophrenia patients (Blasi et al., 2011). Both *DRD2* and *AKT1* were selected as candidate genes for this study, which supports a potential role of these genes in both brain structure and antipsychotic treatment response, in addition to the suggested role in brain function as per the study by Blasi et al. (2011). This warrants future exploration of the potential links between these three traits (brain structure, function, and antipsychotic response) in the context of *DRD2* and *AKT1* variation. As no variants within *AKT1* met the criteria for inclusion in the current study, this gene was not investigated for associations with either ROI volume or antipsychotic treatment response.

4.2. Brain structure in antipsychotic response

Structural variation in the brains of individuals with schizophrenia is undoubtedly correlated with differential response to antipsychotic treatment. Although the exact role that specific brain regions may have in

antipsychotic response remains unclear, this link has been supported by numerous imaging studies (reviewed by Tarcijonas and Sarpal, 2019). It is therefore surprising that no significant associations, nor trends of interest ($P < 0.05$) were identified between antipsychotic response and the brain regions of interest explored in this study, all of which have been previously implicated in varied response to antipsychotic treatment. As with any association studies in a trait of such a complex nature, there are a multitude of reasons for this. Firstly, the participants in this study were first-episode, and treatment-naïve. Neuroimaging studies of antipsychotic response in treatment-naïve patients are incredibly limited, and as antipsychotic treatment results in structural brain changes over time, the effects of prior antipsychotic exposure on brain structure cannot be ruled out in previously treated patients, when making comparisons between studies (Emsley et al., 2017). Furthermore, several studies considered the changes in brain volume between start and endpoint in relation to antipsychotic response (Altamura et al., 2017; Li et al., 2012; Mitelman et al., 2009), whereas this study only included volumetric measures of brain regions at baseline (pre-treatment). Importantly, there are major inconsistencies among studies with regard to the specific antipsychotic administered, the clinical measurements of symptoms, and the criteria for response to treatment, all of which present a massive challenge with respect to study comparison. Additionally, differences in neuroimaging methodologies may also account for inconsistencies between studies. These include differences in instruments used, and data processing methods (i.e. software packages and versions, and parameters used), which contribute to the reliability of structural MRI measures (Gronenschild et al., 2012; Senjem et al., 2005). Lastly, most of the previous studies classified patients as either responders or non-responders, and assessed structural brain differences between the two groups; examples include the studies by Buchsbaum et al. (2003), Mitelman et al. (2009), and Quarantelli et al. (2014). This approach was not feasible for this study, as the majority of participants (~75%) achieved early response, approximately half achieved full remission (~56%), and only nine participants (~9%) were classified as non-responders. The entire patient cohort was therefore assessed together, where response to treatment was based on the treatment trajectory over 12 months, thus taking into consideration all nine of the PANSS score assessments done over this time period. Assessing antipsychotic response in terms of treatment trajectory allows observation of relative differences in response over time between all patients. However, this could possibly explain the lack of significant associations identified here, as differences in brain structure between individuals can be minor and subtle, potentially necessitating the comparison of patients with phenotypic extremes for antipsychotic response, in order to reveal trends in small sample sizes.

4.3. Genetic predictors of antipsychotic response

This study revealed 17 unique significant associations between 10 genetic variants in *CACNA1C*, *NRG1*, and *OXTR*, and different antipsychotic treatment outcomes (Table 3.2). The majority of associations were for the negative symptom domain, and no variants were found to significantly effect changes in positive symptoms over time. Two associations were for changes in general symptoms, and one association was for changes in total symptoms over time. Four of the 10 genetic variants were associated with treatment response across more than one PANSS symptom domain (negative, general, or total), or under both the genotypic and additive allelic models of inheritance. Nine of the variants were novel with respect to antipsychotic treatment response, and the remaining variant (*OXTR* rs4686301) has been previously associated with treatment outcome (Souza et al., 2010)

The abundance of associations pertaining to the negative symptoms of schizophrenia was interesting, as these symptoms are particularly complex and difficult to treat (Millan et al., 2014). The results presented here may therefore have specific links to the pathophysiology and manifestation of negative symptoms such as avolition and blunted emotion, and could potentially be considered as drug targets for the specific improvement of persistent negative symptoms. Considering that 31 of the variants prioritised for investigation in this study had been previously implicated in antipsychotic response (Table S5), it may seem unexpected that only one of these variants was significantly associated with antipsychotic treatment outcome in our study. However, this did not come as a surprise when taking into account the previously discussed clinical and methodological inconsistencies between studies, which render study comparison difficult, and create a massive challenge with respect to the reproducibility of findings. In addition to these factors, another important consideration warrants attention in the context of genetic association studies: that of population stratification (Daya et al., 2013). The current study cohort predominantly comprised South African Mixed-Ancestry individuals, who are highly admixed, yet the vast majority of previous genetic studies of treatment response identified were done in non-African populations. When comparing genetic associations across different population groups, one needs to consider the fluctuations in allele frequencies between populations that lead to differences in LD. This is demonstrated in particular with the extensive variation in LD patterns between individuals of European and African descent (Gurdasani et al., 2019; Sirugo et al., 2019). This contributes to the inconsistencies observed among genetic association studies, as variants associated with a certain phenotype in a specific population group, could just be proxies for the biologically relevant variants due to LD (Sirugo et al., 2019). This phenomenon emphasises the importance of conducting genetic association studies in more genetically diverse population groups, as 1) variants associated with certain outcomes in European individuals may not be applicable in African individuals (Gurdasani et al., 2019; Sirugo et al., 2019), and 2) populations with high levels of genetic diversity present an untapped recourse with regard to the discovery of potential biologically relevant variants, due to the low levels of linkage disequilibrium (Gurdasani et al., 2019).

4.3.1. Calcium channel signalling and CACNA1C *variation*

Two novel significant associations between *CACNA1C* variants and antipsychotic treatment response were identified (rs10161032 and rs215976; Table 3.2). Considering the critical role of ionic calcium in neuronal function and neurotoxicity (Harrison et al., 2019), calcium channel signalling, modulated by voltage-gated calcium channels, is gaining increasing recognition for its implication in the pathophysiology of neuropsychiatric disorders including schizophrenia (Bhat et al., 2012; Kabir et al., 2017), as well as its excellent potential for therapeutic intervention (O'Connell et al., 2019; Zamponi, 2016). Calcium channel blockers have been used in the treatment of cardiovascular conditions for 40 years, and are emerging as potential therapies for a number of neuropsychiatric disorders including schizophrenia (Grebb et al., 1986; Harrison et al., 2019; Price, 1987; Yamada et al., 1996). These drugs primarily target L-type voltage-gated calcium channels (Harrison et al., 2019), of which subunit alpha-1C (encoded by *CACNA1C*) is one of the main subtypes expressed in the brain (Kabir et al., 2017). Additionally, the alpha-1C subunit is essential for normal brain development and plasticity (Kabir et al., 2017), and for these reasons, *CACNA1C* has been the most widely documented with regard to psychiatric disorders (Bhat et al., 2012; Kabir et al., 2017), as well as for association with antipsychotic treatment response (O'Connell et al., 2019; Porcelli et al., 2015; Yu et al., 2018).

With respect to the first significant variant, rs10161032, the *CC* genotype was associated with worse response to treatment compared to *TT*, considering the trajectory of both general and negative symptoms over time. This was further supported by the association of each additional *C* allele conferring a worse general symptom trajectory over time, under the additive model (Table 3.2). This variant was predicted to be involved in both proximal and distal regulation according to rSNPbase, and is also within a transcription factor binding motif for EHF (ETS homologous factor). Interestingly, a variant in *EHF* (rs286913) was the most significant variant in a genome-wide pharmacogenomic study looking at neurocognitive phenotypes as indicators of antipsychotic response, where it was found to significantly mediate the effects of ziprasidone on vigilance (McClay et al., 2011). EHF is known to be a transcriptional repressor downstream of mitogen-activated protein kinase (MAPK) signalling cascades (Tugores et al., 2001). Abnormal activity of MAPK-associated signalling pathways has been found in frontal cortical areas of the post-mortem brain in schizophrenia (Funk et al., 2012). EHF could therefore be a relevant transcription factor to explore further in the context of antipsychotic response, as in addition to its role in MAPK signalling, and its potential contribution to neurocognition, our findings suggest an additional role for EHF in antipsychotic response via the regulation of calcium channel signalling through *CACNA1C* binding.

The second *CACNA1C* variant, rs215976, was found to be associated with an improved trajectory for negative symptoms with each additional *T* allele. This variant was predicted to be missense/ synonymous according to the Ensembl variant effect predictor, resulting in a predicted amino acid change (aspartic acid to glutamic acid) as per the SIFT and Polyphen results from SNPnexus. However, the consequences of this amino acid change are inconclusive, as it was predicted by SIFT to be tolerated, and a number of results were returned for Polyphen, with predictions ranging from benign (scores from 0 to 0.084), to probably damaging (scores from 0.919 to 0.997). Further investigation is required to confirm whether this variant has a damaging functional consequence, as such alterations to the protein structure may potentially be beneficial in the context of antipsychotic mechanism of action, thus contributing to improved response to treatment.

Although *in silico* prediction tools provide a useful platform to predict the potential consequences of variants, the suggested mechanisms by which the aforementioned variants may contribute to alterations in calcium channel signalling are by no means indisputable. These findings require validation in other cohorts, and predicted consequences of variants should be functionally validated *in situ* or *in vivo*. That said, these results lend further evidence to the involvement of *CACNA1C*, and calcium channel signalling, in antipsychotic efficacy and response. The novel associations warrant further investigation in research pertaining to antipsychotic response, especially considering the recognised potential for calcium channels as therapeutic targets.

4.3.2. NRG1-ErbB4 signalling and NRG1 *variation*

Of the variants significantly associated with treatment outcome in this study, the majority (six of the 10) were *NRG1* variants (Table 3.2). *NRG1* (encoding neuregulin 1) is a pleiotropic growth factor with multiple isoforms, that plays a role in neurodevelopment and synaptic plasticity, and is also one of the leading schizophrenia susceptibility genes (Deng et al., 2013; Harrison and Law, 2006). ErbB4 is the receptor for NRG1, and NRG1-ErbB4 signalling has been shown to closely interact with several neurotransmitter pathways that are critical in schizophrenia pathophysiology and antipsychotic efficacy, namely glutamatergic, GABAergic, and

dopaminergic pathways (Deng et al., 2013). The NRG1-ErbB4 signalling pathway may therefore present an opportunity for the discovery of novel therapeutic targets for schizophrenia treatment (Deng et al., 2013; Hahn, 2011; Karam et al., 2010).

All of the *NRG1* variants significantly associated with treatment response had predicted roles in gene regulation according to RegulomeDB, rSNPBase, or SNP2TFBS. The abundance of variants with regulatory consequences does not come as a surprise, as it has become increasingly apparent that significant associations in GWAS of complex disorders such as schizophrenia, as well as antipsychotic response, are enriched for variants in noncoding regions of the genome (Ovenden et al., 2017; Roussos et al., 2014). Noncoding variants involved in regulatory pathways have implications in altered gene expression and may contribute larger effects than variants in coding regions, considering their influence on global transcription and translation (Georgitsi et al., 2011). The variant with the lowest RegulomeDB score of 1f (likely to affect binding and linked to expression of a gene target) was predicted to be a *cis*-eQTL according to RegulomeDB and rSNPBase, thus directly influencing *NRG1* expression. This variant (rs2439312) therefore had the most evidence for regulatory impact and was significantly associated with improved negative symptomology over time. Interestingly, this variant was found to be in LD with rs17645417 (predicted to be less likely to affect binding according to RegulomeDB), which was the variant with the highest number of significant associations with antipsychotic response. These associations showed that both the *CC* and *CT* genotypes had significantly worse treatment trajectories for negative symptoms, than the *TT* genotype. Furthermore, under the additive allelic model, it was found that each additional *C* allele conferred significantly worse treatment trajectories for both negative and total symptom scores over time. It was unexpected to see such different associations for two variants in LD, yet not unjustifiable, as these two variants had a D' value of 0.84 and were therefore not in perfect LD, which could explain the differences between the associations.

Collectively, these results give an indication that dysregulation of neuregulin 1 signalling, that may arise from multiple rSNPs in *NRG1*, could contribute toward phenotypic variation in antipsychotic treatment response. These findings therefore support the existing evidence for the role of NRG1-ErbB4 signalling in variable response to antipsychotics (Kampman et al., 2004). Furthermore, the novel associations discovered here warrant further investigation, as this could provide additional insight into the role of NRG1-ErbB4 signalling in treatment response, and as a potential target for novel therapeutic intervention.

4.3.3. Oxytocin signalling and OXTR *variation*

Two significant associations between *OXTR* variants and antipsychotic response were identified (Table 3.2), one novel association (rs237884) and one that had been previously reported in literature (rs4686301; Souza et al., 2010). The *OXTR* gene encodes the oxytocin receptor protein (OXTR) in humans which functions as a receptor for the neurohormone oxytocin (Chatterjee et al., 2016). Although only one previous study of *OXTR* variants in antipsychotic response was identified (Souza et al., 2010), the oxytocin system has received considerable attention in the context of psychiatric disorders (Rich and Caldwell, 2015; Quintana et al., 2019). Of particular relevance here, is the traction that is being gained for the oxytocin system as a promising therapeutic target in schizophrenia (Bujanow, 1972; MacDonald and Feifel, 2012; Rich and Caldwell, 2015). This has been explored in animal studies (Keebaugh et al., 2015; Lee et al., 2005; 2008), as well as several

small clinical trials in humans (Feifel et al., 2010; Lee et al., 2013; Modabbernia et al., 2013; Pedersen et al., 2011). Oxytocin signalling serves as an attractive candidate for drug targeting because of its diverse range of actions (Chatterjee et al., 2016).

In the study of *OXT* (encoding oxytocin) and *OXTR* variants in antipsychotic response by Souza and colleagues in 2010, the *TT* genotype of *OXTR* rs4686301 was found to be nominally associated with improvement of positive symptoms (Souza et al., 2010). Conversely, an association between a worse treatment trajectory for negative symptoms with each additional *T* allele of rs4686301 was identified in the current study (Table 3.2). There are a number of explanations for the contrasting associations between the two studies. Firstly, the difference between positive and negative symptoms must be acknowledged when considering response to antipsychotic treatment. Regardless of the varying clinical assessment tools used to measure and categorise the symptoms of schizophrenia, the negative symptoms (i.e. avolition and anhedonia) tend to persist even when positive symptoms have been alleviated. Considering the inconsistent effects of antipsychotics between distinct symptom domains, contrasting directionality of response observed for a particular variant in positive and negative symptom domains in different studies is therefore not unjustifiable. Secondly, the study by Souza et al. (2010) was done in a cohort comprising mostly individuals of Caucasian descent (82%), whereas 80% of the individuals in the current study were South African Mixed-Ancestry. As discussed in section 4.3, population stratification may account for some of the observed inconsistencies between studies considering different population groups. Lastly, the study by Souza et al. (2010) was investigating clozapine response, therefore almost all patients in the study had been classified as treatment refractory or intolerant of FGA treatment. This is in contrast to the current study of flupenthixol treatment response (an FGA) in FES patients. This is particularly notable here, as treatment refractoriness may represent a distinct subtype of schizophrenia, with clozapine used for antipsychotic therapy in these patients when other drugs fail. This could, in part, explain how the *T* allele of rs4686301 conferred worse response to treatment in a first-episode cohort, yet the *TT* genotype conferred improved clozapine response in the treatment refractory cohort.

A second variant within *OXTR*, rs237884, was significantly associated with treatment response in our study under both the genotypic and additive inheritance models. Here, individuals with the *GG* genotype for this variant had a significantly improved treatment trajectory in the negative symptom domain, compared to individuals with the *AA* genotype. This was in accordance with the additive model, which showed that each *G* allele of rs237884 conferred an improvement in treatment trajectory for the negative symptoms. Interestingly, this variant was predicted to alter miRNA binding (according to PolymiRTS), where it was shown to be located within the target site for *hsa-miR-4786-3p*. Here, the presence of the *G* allele predicted binding of *hsa-miR-4786-3p*, whereas the *A* allele could abolish this target site. The predicted regulatory impact of rs237884 lends evidence to the potential role of miRNA-mediated regulation in antipsychotic treatment response.

These findings therefore provide support for the implication of rs4686301 in antipsychotic response, although this variant could contribute varying effects with different antipsychotics, or with different subtypes of schizophrenia. A novel *OXTR* association was also identified which warrants further investigation, but could potentially corroborate the potential for miRNA-mediated regulation as a mechanism contributing to the functioning of the oxytocin system, and by extension, to antipsychotic response. These results should be

investigated further, as this could contribute to our understanding of the oxytocin signalling as a potential drug target for schizophrenia treatment.

4.3.4. Imaging genetics of antipsychotic response

The lack of significant associations between genetic variants and ROI volumes prevented the identification of significant imaging genetic correlates of antipsychotic treatment response in this study. This can most likely be attributed to insufficient statistical power, considering the limited sample size in this study. However, this study was exploratory in nature, therefore an uncorrected significance threshold ($\alpha = 0.05$) was considered in order to examine imaging genetic trends of interest for antipsychotic response. Three of the genetic variants found to be significantly associated with antipsychotic response in this study, showed trends of interest for ROI volume ($P < 0.05$; Table 3.3). These variants were *CACNA1C* rs10161032, *OXTR* rs237884, and *NRG1* rs2439312. The *CC* genotype and number of *C* alleles for *CACNA1C* rs10161032, which were significantly associated with worse response to antipsychotic treatment under the genotypic and additive inheritance models (respectively), revealed potential trends for larger caudate and subcortical grey matter volumes. The *GG* genotype and number of *G* alleles for *OXTR* rs237884 were associated with improved response to treatment in this study, and also showed trend-level reductions in putamen volumes under both inheritance models. Lastly, *NRG1* rs2439312 showed a potential trend for larger cortex and total grey matter volumes with each additional *T* allele, for which there was a significant association with improved treatment outcome.

As all previous imaging genetics studies of antipsychotic response involved the investigation of functional magnetic resonance imaging (fMRI) measures, no comparisons could be made with these studies (Bishop et al., 2015; Blasi et al., 2011; 2015). Furthermore, none of the three variants discussed here have been previously associated with volumetric variation in any of the brain regions of interest. Despite the lack of significant associations, these results suggest that at least three of the variants implicated in differential response to antipsychotics in this study, may potentially influence brain structure as well, and should be further investigated for potential associations with volumetric variation in brain ROIs. Considering that to the best of our knowledge, this was the first study to investigate the genetic overlap between structural neuroimaging measures and antipsychotic response in schizophrenia, these findings could provide a starting point for future structural imaging genetics studies of antipsychotic treatment outcome.

4.4. Childhood trauma in antipsychotic response and brain structure

Although the severity of childhood trauma was not significantly associated with differential treatment response in our study, when considering an uncorrected significance threshold ($\alpha = 0.05$), a trend of interest was observed. This suggested that more severe experiences of emotional neglect during childhood may contribute to a poorer treatment trajectory for positive symptoms. In a previous study of treatment-resistant schizophrenia, it was reported that more frequent experiences of emotional neglect and abuse, as well as sexual abuse, were evident among the treatment-resistant patients compared to the patients who responded to antipsychotics (Hassan and De Luca, 2015). It has also been shown that childhood trauma, and emotional abuse in particular, may contribute to early non-response to antipsychotic treatment in FES patients (Misiak and Frydecka, 2016). The paucity of studies addressing the link between childhood adversities and treatment outcome makes it

difficult to draw unequivocal conclusions, however there is an apparent trend among the existing literature for less favourable response to antipsychotic treatment in patients with a self-reported history of childhood trauma. Although our findings were not statistically significant, the trend identified does support previous findings.

In terms of childhood trauma and brain structure, no significant associations, nor trends of interest were identified in this study for the eight ROIs. Potential trends between antipsychotic response and ROI volumes in the context of childhood trauma could therefore not be explored in our cohort. The majority of previous studies investigating the link between brain volume and childhood trauma have focussed on the hippocampal and amygdalar brain regions (Calem et al., 2017; Misiak et al., 2017). It has been suggested that these regions in particular could mediate associations between early trauma and schizophrenia due to their implication in hypothalamic-pituitary-adrenal (HPA) axis regulation, which is the body's core stress response system (Misiak et al., 2017). As the amygdala was not found to be previously associated with antipsychotic response, it was not included as an ROI for this study. However, an association with the hippocampus was expected, as reduced hippocampal volume is one of the most consistently reported neuroimaging correlates of childhood trauma (Calem et al., 2017; Teicher and Samson, 2016). In addition to this, sexual abuse has been previously associated with reduced total grey matter volume (Sheffield et al., 2013), which was also included in this study, yet no associations were identified here. The numerous clinical and methodological inconsistencies among studies that could explain either contrasting associations, or lack of associations in our study, have already been discussed. One additional clinical inconsistency that has not yet been mentioned is that of childhood trauma assessment. Differences in the measurement tools used to assess the severity of different types of childhood trauma range from structured and semi-structured interviews to self-report questionnaires, thereby potentially hindering the reproducibility of findings (Popovic et al., 2019).

4.5. Toward a unified view of antipsychotic treatment outcome

4.5.1. Gene-environment interactions (GxE) in antipsychotic response

When considering GxE, thirty-four variants in *CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR* were significantly associated with antipsychotic response when interacting with childhood trauma (Tables 3.4 and 3.5). These associations show that childhood trauma can influence response to antipsychotic treatment via interactions with certain genetic variants. In other words, the way an individual responds to treatment based on the presence of specific genotypes, can be altered if certain types and severities of trauma are experienced during childhood. Most of these associations were for changes in negative symptoms over time, and no significant associations were identified in the positive symptom domain. Several associations were evident for the general symptom domain, as well as for changes in total symptom severity scores over time. This is the same as what was observed in the genetic association analyses, when childhood trauma was not factored in. Each of the five CTQ subscales, namely emotional abuse and neglect, physical abuse and neglect, and sexual abuse, as well as overall trauma, were involved in these significant GxE. However, predominantly sexual abuse was found to significantly influence patients' response to treatment based on genotypic differences.

With regard to the genetic variants significantly associated with antipsychotic treatment response when childhood trauma was not factored in (Table 3.2), it was interesting to see that only one of these variants

remained significant in the GxE analysis (*NRG1* rs6987996), even though many more variants were significantly associated with treatment response when interacting with childhood trauma (Tables 3.4 and 3.5). This observation also highlights the fact that all, but one, of the significant variants in the GxE analysis were not found to significantly influence treatment response when childhood trauma was not considered. Four of the seven *COMT* variants in the significant GxE, have been associated with antipsychotic response in previous studies (rs737865 and rs4818; Gupta et al., 2009), or according to the PharmGKB database (rs2020917 and rs933271). Interestingly, these variants were only significantly associated with treatment response in our cohort when the severity of childhood trauma was factored in. The same was observed for *OXTR* rs11706648 (Souza et al., 2010), *DRD3* rs6280 (Escamilla et al., 2018) and *DRD3* rs167771, which was not implicated in antipsychotic response, but in antipsychotic toxicity (extrapyramidal symptoms), according to PharmGKB. The number of previously reported variants here was particularly notable, considering that in the genetic analyses (without childhood trauma), only one of the significant variants had been previously associated with antipsychotic response in literature (*OXTR* rs4686301). This emphasises the importance of childhood trauma as a relevant modifier to include in analyses of antipsychotic response. In terms of predicted consequences of the variants involved in the significant GxE, *NRG1* rs3924999 was predicted to be missense according to Ensembl, with inconsistent effect predictions across SNPnexus, SIFT, and Polyphen-2 ranging from “tolerated/ benign” to “possibly damaging/ deleterious”. *DRD3* rs6280 was also predicted to be missense according to Ensembl, yet reported as “tolerated/ benign” across all aforementioned prediction tools. The remainder of the variants had predicted regulatory effects, which provides support for the consideration of regulatory variants in future GxE studies of antipsychotic response, as well as complex disorders and neuroimaging phenotypes, seeing as the majority of existing GxE studies only consider coding variants.

Upon overall inspection of the results, it is apparent that many of the variants in the GxE are in LD with another variant in the same gene (Tables 3.4 and 3.5). There are many more cases of LD between these variants than the variants that were significantly associated with antipsychotic response before childhood trauma was factored into the analyses (Table 3.2). However, the LD reported for the GxE variants is based on the initial LD analysis that was done for the entire cohort (N = 103), whereas the GxE analyses were done using the subset of participants for which CTQ data was available (N = 75). Because of the small cohort size, fluctuations in sample sizes between the various analyses will result in variation in allele frequencies and LD patterns. These variants may therefore not be in LD (or not strong enough LD) with one another, when only considering these 75 patients, which would explain the observed differences between associations involving these variants. An example of two variants in very strong LD, resulting in identical effect sizes and P values for the respective associations, can be seen with the *COMT* variants rs737865 and rs737866. No other cases like this were evident. Considering that the probability of strong LD being calculated between two variants increases with a decrease in sample size, our limited sample size means that variants found to be in LD based on D’ values may not be biologically linked. For this reason, and due to the fluctuating sample numbers between different analyses, no variants were initially eliminated based on LD, as biologically relevant variants may have been overlooked in downstream analyses.

Considering Hardy-Weinberg equilibrium, *CACNA1C* rs2238096 was the only significant variant found to deviate from HWE principles. It is generally accepted that a deviation in HWE could confer association with a trait, disease, or disorder being investigated (Wittke-Thompson et al., 2005). A common observation in case-

control association analyses is the occurrence of variants that deviate from HWE in the case group, but meet HWE assumptions in controls, or vice versa. This suggests either increased susceptibility, or resilience to the disorder, respectively (Wittke-Thompson et al., 2005). It is therefore possible that the observed deviation of rs2238096 from HWE could be attributed to increased risk for schizophrenia, however the lack of a control group in this study prevents evidence-based speculation in this regard. Furthermore, common trends of HWE and deviation thereof, are not as well characterised in complex disorders such as schizophrenia, as opposed to more common disease models (Wittke-Thompson et al., 2005). This observed significant association should therefore be regarded tentatively, as other reasons for the HWE deviation include possible genotyping error, gene-gene interactions, age, gender, and population stratification (Wigginton et al., 2005). However, all of our association analyses were adjusted for differences in age, gender, and ancestry.

Noticeably, there are more than three times the number of significant associations here, than in the analyses where only genetic variants (without factoring in childhood trauma) were considered, even with a significance threshold that was six times more stringent to account for additional testing across the different CTQ scoring domains. From a statistical standpoint, this suggests that incorporating relevant environmental influences into genetic analyses of complex traits may increase power to find associations. Moreover, not taking into account these environmental factors may put into question the biological validity of findings, given the tendency of childhood trauma to modulate the effects of genetic variants associated with disorder risk/ manifestation (Alemany et al., 2015; Collip et al., 2013; Green et al., 2014; 2015; Modinos et al., 2013), or response to antipsychotic treatment (McGregor et al., 2018). This was demonstrated in this study with one variant, *NRG1* rs6987996. This variant was found to be significantly associated with a worsened negative symptom trajectory for patients with a *TT* genotype compared to *CC* patients, or for each additional *T* allele. However, when considering the severity of childhood trauma, the directionality of this effect was altered, where it was found that *TT* individuals show improved response to treatment compared to *CC* individuals (also for negative symptoms), specifically with increased severity of physical neglect, and overall trauma experienced during childhood. This implies that the *TT* genotype of this variant could contribute to protective mechanisms in the context of the negative biological consequences induced by childhood trauma. This phenomenon was observed in a study by McGregor et al. (2018), with a haplotype in *MMP9*. Here, it was suggested that this could possibly be explained by the process of synaptic scaling, which is a form of homeostatic plasticity (McGregor et al., 2018).

Hebbian synaptic plasticity includes long-term potentiation (LTP) and long-term depression (LTD), which are forms of long-lasting activity-dependent alterations in synaptic strength (Cooke and Bliss, 2006; Malenka and Bear, 2004). However, the occurrence of positive feedback loops brought about by these activity-dependent changes in synaptic strength can provoke destabilisation of neural networks (Fernandes and Carvalho, 2016). In order to counteract this, negative feedback control of excitatory synapse strength is triggered, thereby stabilising the rate of neuron firing (Citri and Malenka, 2008; Fernandes and Carvalho, 2016). This mechanism is known as homeostatic plasticity, or synaptic scaling, and is essential in maintaining neuronal activity within appropriate ranges for normal brain functioning (Fernandes and Carvalho, 2016). There is emerging evidence to support the potential role of disrupted synaptic scaling in the development of neuropsychiatric disorders such as schizophrenia (Sellgren et al., 2019), yet the potential link to antipsychotic response remains relatively unexplored. In the context of a link to childhood trauma, it has been hypothesised that early trauma exposure

triggers gene expression promoting a form of synaptic modelling that is less responsive with following exposure to traumatic events (McGregor, 2014). However, this is believed to depend on the age at which trauma is experienced (McGregor, 2014).

With this in mind, considering GxE, the results of this study suggest that some genetic profiles may confer more resilience to early-life traumatic experiences than others, and this could be due to the involvement of certain genes in pathways essential to synaptic plasticity. Conversely, variants contributing to aberrant expression of genes central to synaptic plasticity mechanisms, could result in insufficient stabilisation of neuronal activity in the context of provocation by traumatic events, thereby contributing to unfavourable response to antipsychotic treatment. This hypothesis is supported when considering the specific GxE associations highlighted in this study, as all of the genes involved in these associations (*CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR*) have shown evidence for potential involvement in mechanisms of synaptic plasticity (Forero et al., 2006; Guma et al., 2019; Moon et al., 2018; Lin and Hsu, 2018; Shamir et al., 2012; Tropea et al., 2018), as well as differential antipsychotic response (Bourgon et al., 2016; Gupta et al., 2009; Jajodia et al., 2016; O'Connell et al., 2019; Souza et al., 2010; Vehof et al., 2012).

4.5.2. Pathway involvement in antipsychotic response

All of the genes that were significantly associated with antipsychotic treatment response without childhood trauma (*CACNA1C*, *NRG1*, and *OXTR*; Table 3.2) were also implicated in antipsychotic response in the GxE analyses with childhood trauma, along with *COMT*, *DISC1*, and *DRD3* (Tables 3.4 and 3.5). These genes (*CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR*) were therefore considered as the most notable genes with respect to antipsychotic treatment response in this study and were used to identify potential pathways of interest. Of the 33 pathways identified via Enrichr analysis, no pathways involving *DISC1* were returned, but each of the remaining genes was involved in at least one pathway (Table 3.7). The five most significant pathways according to *P* value (involving more than one gene) were the "Dopaminergic synapse" (*CACNA1C*, *COMT*, *DRD3*), "Oxytocin signalling pathway" (*OXTR* and *CACNA1C*), "Calcium signalling pathway" (*OXTR* and *CACNA1C*), "cAMP signalling pathway" (*OXTR* and *CACNA1C*), and "Neuroactive ligand-receptor interaction" (*OXTR* and *DRD3*). Notably, 29 of the pathways involved *CACNA1C*, and each of the top five pathways either involved *CACNA1C*, *OXTR*, or both of these genes.

Calcium channel alpha-1C subunit, encoded by *CACNA1C*, is involved in modulating the activation of intracellular signalling pathway activity, gene transcription, and synaptic plasticity (Moon et al., 2018). This arises from cell membrane depolarisation coupled to an increase in membrane permeability, resulting in calcium influx (Moon et al., 2018). Furthermore, L-type calcium channel antagonists have been shown to decrease induction of LTP in the CA1 of the hippocampus in rats (Freir and Herron, 2003), and alpha-1C knockdown models have shown reduced hippocampal LTP (Moosmang et al., 2005), emphasising the importance of calcium channel signalling in synaptic plasticity. With regard to *OXTR*, early-life exposure to trauma has been found to dysregulate the developing oxytocin system, which adversely affects many of the functions that are central to oxytocin regulation, including the regulation of emotion and stress (Nylander & Roman, 2012). Furthermore, *OXT* (encoding oxytocin) has been repeatedly shown to modify synaptic properties and plasticity both *in vitro* and *in vivo* (Rajamani et al., 2018). Overall, these findings highlight *OXTR*

and *CACNA1C* as genes of particular interest with respect to the link between antipsychotic response and GxE with childhood trauma. As these two genes are common to both the oxytocin and calcium signalling pathways, among other pathways, future studies could potentially investigate *OXTR* and *CACNA1C* together with respect further exploration of these genes in synaptic plasticity, stress-response mechanisms, and antipsychotic response. This could provide further insight into the mechanistic links between GxE and differential response to antipsychotics, and possibly highlight relevant pathways to investigate for novel therapeutic targets.

4.5.3. Imaging gene-environment interactions (iGxE) in antipsychotic response

As there were no significant associations between GxE and ROI volumes, no significant iGxE of antipsychotic response were idetified. However, when considering an uncorrected significance threshold ($\alpha = 0.05$), numerous trends of interest were identified between GxE and ROI volumes. Fourteen of these involved GxE interactions that were found to be significantly associated with antipsychotic response in this study, which allowed us to draw tentative comparisons between the results (Table 3.6). Upon first inspection of these results, it was immediately noticeable that there was a consistent trend between antipsychotic treatment response and ROI volumes, in the context of GxE with childhood trauma. Here, where trends for larger ROI volumes were observed with specific GxE, significantly improved treatment response would be evident for the same GxE, and vice versa. For example, considering the interaction between increased severity of sexual abuse and *CACNA1C* rs4126711, the *TC* genotype showed a trend for reduced putamen volume, and was significantly associated with worse treatment response for negative symptoms. This was supported in the opposite direction, where the *AA* genotype of *DISC1* rs701160 showed a trend for larger putamen volume, and was significantly associated with improved treatment response for negative symptoms, when increased severity of sexual abuse was evident. These results therefore highlighted a positive correlation between baseline ROI volumes and antipsychotic response, when considering associations with common GxE. Interestingly, when childhood trauma was not factored in, no such trends were apparent, and inconsistent directionality was observed between ROI volumes and treatment response in the context of genetic associations.

Considering the association analyses between ROI volumes and antipsychotic treatment response in this study, no significant associations, nor trends of interest, were identified (section 3.6.1). The positive correlation between ROI volumes and antipsychotic response that was highlighted in the context of GxE, was therefore not comparable with direct associations between the two. However, when considering previous imaging analyses of antipsychotic response, this correlation has been observed in many studies, showing evidence among the literature for increased ROI volumes conferring improvement in antipsychotic response. Furthermore, there is supporting evidence for this correlation in each of the regions of interest highlighted in this study, namely the caudate (Hutcheson et al., 2014), cortex (Zipursky et al., 1998a), hippocampus (Savas et al., 2002), pallidum (Hutcheson et al., 2014), putamen (Buchsbaum et al., 2003; Hutcheson et al., 2014), subcortical grey matter (Molina et al., 2010), and total grey matter (Altamura et al., 2017). For example, it was found that with a decrease in hippocampal volume, worse response to risperidone was observed (Savas et al., 2002). Here, the authors mentioned a previous study suggesting that risperidone mechanism of action involved reduced hippocampal activity along with decreased feedback via cortico-striato-thalamic loops (Liddle

et al., 2000; Savas et al., 2002). The authors suggested that this finding could indicate that the hippocampus should be large enough to be receptive to the mechanisms of risperidone (an SGA), conferring proper response to this treatment (Savas et al., 2002). No similar mechanisms could be identified for flupenthixol (an FGA) in our study. Interestingly, reduced hippocampal volume is the most consistently reported neuroimaging correlate of schizophrenia (Ebdrup et al., 2010), as well as of childhood trauma (Calem et al., 2017; Teicher and Samson, 2016). These findings suggest that the manifestation of schizophrenia symptoms, and subsequent poor response to antipsychotic treatment, may arise from decreases in hippocampal neuromediators and their receptors (Savas et al., 2002). Furthermore, treatment with antipsychotics can lead to increases in the volume of several brain regions over time, indicating response to treatment (Chakos et al., 1994; Emsley et al., 2017; Gur et al., 1998). However, these affects appear to be region-specific, as reductions in total brain volume have also been observed for medicated patients compared to antipsychotic naïve patients, with further discrepancies reported for typical compared to atypical antipsychotics (Haijma et al., 2013). Considering findings of antipsychotic-induced volume increases, it was found that volume expansion in the putamen was correlated with PANSS score reduction ratio, suggesting that increased expansions in putamen volume over treatment periods may be indicative of improved response to treatment (Li et al., 2012). Overall, imaging studies have found reduced brain volume in schizophrenia patients compared to healthy individuals (Krause and Pogarell, 2017), believed to be developmental in origin. Studies have also found that greater deficits in grey matter volumes are related to worse cognitive performance (Sullivan et al., 1996; Zipursky et al., 1998b). The links between more severe patterns of atrophy in schizophrenia, impaired brain functions, and more severe disorder pathogenesis, may therefore represent a fixed deficit that could confer reduced responsivity to antipsychotics (Molina et al., 2010; Zipursky et al., 1998a).

Another interesting consideration here, is the link between childhood trauma and reductions in specific ROI volumes in some studies (Calem et al., 2017; Misiak et al., 2017; Teicher and Samson, 2016), as well as worse treatment outcome in schizophrenia (Misiak and Frydecka, 2016; Hassan and De Luca, 2015). Even though this was not reflected in the results of this study, these previously identified relationships lend evidence to the potential involvement of childhood trauma in the correlation between ROI volumes and antipsychotic response. Moreover, previous studies have shown that the relationships between early trauma and ROI volumes/ antipsychotic response can be modulated by genotypic differences for certain variants (Aas et al., 2013; Frodl et al., 2014; McGregor et al., 2018). Therefore, despite the lack of statistical significance between GxE and ROI volumes in this study, the novel GxE identified here suggest a mechanism through which the relationship between baseline ROI volumes and antipsychotic response may be mediated. In other words, it can be postulated that in some cases, increases in early life trauma may lead to decreases in ROI volumes, which could contribute to less favourable response to antipsychotic treatment, and that this process could be modulated by genotypic variation that confers either vulnerability or resilience to stress. If this is true, when considering brain structure as an intermediate phenotype of antipsychotic response, then the same (relevant) GxE that contribute to variation in brain structure, should predict the corresponding differences in antipsychotic response, which was observed in this study. Importantly, this is not an attempt to oversimplify an incredibly complex system, but rather a depiction of at least one of the processes taking place in the path from genetic architecture to variable antipsychotic treatment response (Figure 4.1). There are numerous other known, and unknown, mechanisms involved here that were not explored in this study. For example, in a comprehensive review of epidemiological, clinical, neuropsychological, and biological findings focussing on the link between

childhood trauma and psychosis, a simplified overview of trajectories leading from childhood trauma to psychosis was presented (Figure 4.2; Misiak et al., 2017). Although this was not specifically focussed on treatment response in schizophrenia, many of the factors presented here, including biological alterations that arise from GxE with childhood trauma, may also contribute to poor outcome in patients, and are therefore relevant to consider.

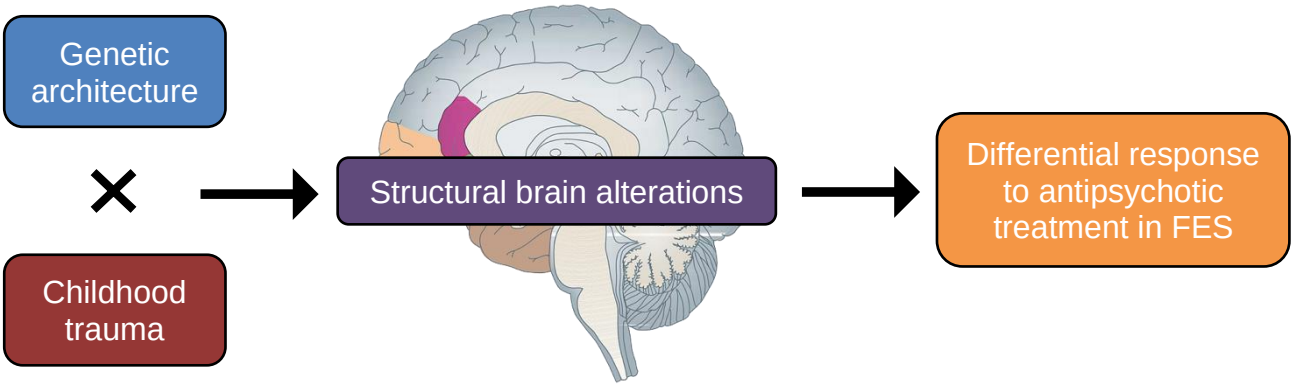


Figure 4.1. A simplified depiction of one potential biological course from GxE to differential antipsychotic treatment response, where there is evidence for a positive correlation between structural brain alterations and antipsychotic response, i.e. increased ROI volumes conferring improved response to treatment, and vice versa.

In the future, the accurate prediction of antipsychotic treatment response will most likely rely on multi-faceted patient profiles. Better characterisation of the relationships between multiple correlates of antipsychotic response, and the biological mechanisms underlying these relationships, is therefore crucial for the progression toward more personalised treatment strategies in schizophrenia. To this end, the significant associations and novel exploratory trends identified in this study provide support for the utility of integrative research approaches to more effectively disentangle some of the underlying mechanisms at play. That said, there is still a tremendous amount of research to be done in order to unpack the complex systems contributing to treatment outcomes. However, considering a more unified view of antipsychotic treatment response, and utilising integrative research approaches to more effectively capture this view, may contribute to the progress toward more individualised therapeutic interventions.

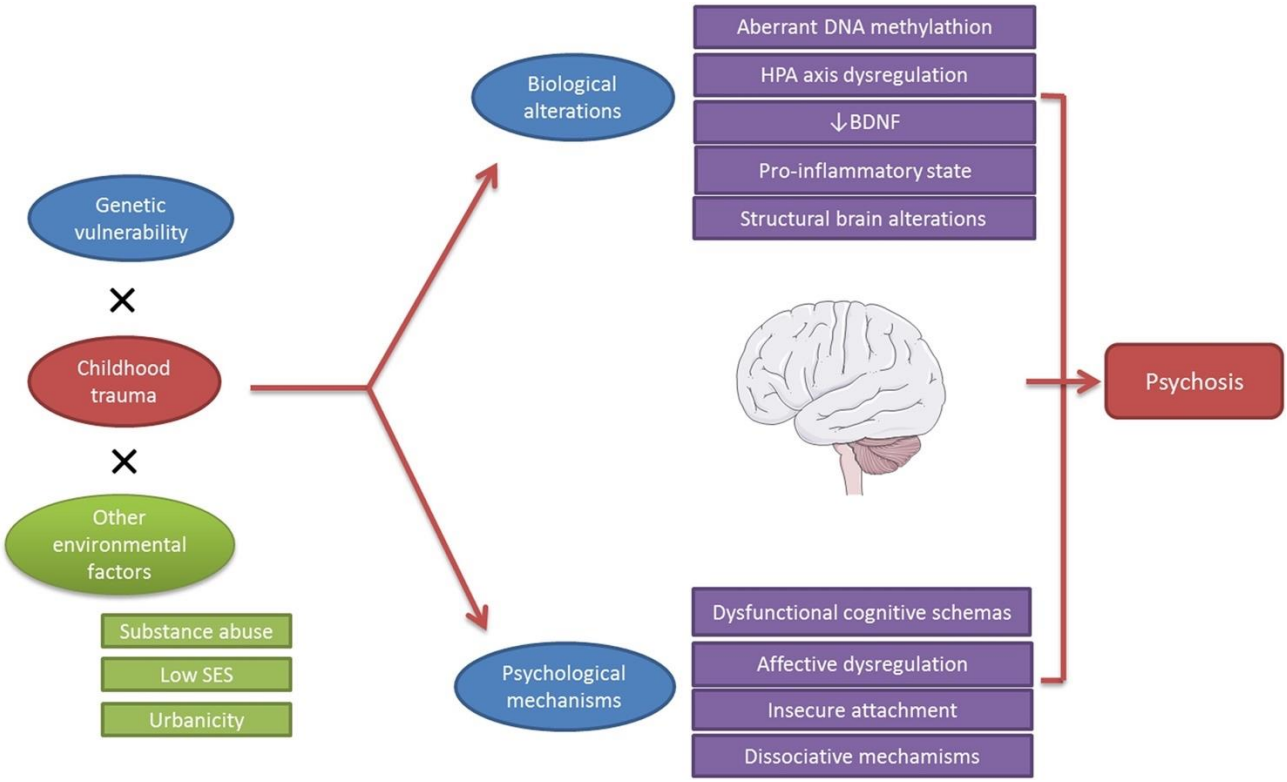


Figure 4.2. A simplified overview of trajectories leading from childhood trauma to psychosis (Misiak et al., 2017). Childhood trauma and other environmental factors, including substance abuse, low socioeconomic status (SES) or high urbanicity, may contribute to psychosis risk via interactions with genetic vulnerability. Furthermore, childhood trauma may increase psychosis risk via distinct biological alterations, including aberrant DNA methylation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, decreased levels of brain-derived neurotrophic factor (BDNF) or subclinical pro-inflammatory states observed in parallel to structural brain alterations. Experiences of child maltreatment might also increase the risk for developing psychosis via psychological mechanisms, such as dysfunctional cognitive schemas, affective dysregulation, insecure attachment and dissociation (Misiak et al., 2017). *Reproduced with permission from Elsevier.*

CHAPTER 5

Conclusions, limitations, and future prospects

5.1. Conclusions

The aim of this study was to better characterise the interplay between multiple known correlates of antipsychotic response, namely genetics, brain structure, and childhood trauma. This was done by performing association analyses in a stepwise fashion, ending with GxE analyses of antipsychotic response and ROI volumes. Although each separate component of this study had been investigated to some extent in existing literature, to our knowledge this was the first study to incorporate all correlates in an attempt to explore a more holistic view of antipsychotic treatment response.

This study provided support for the involvement of several candidate genes in antipsychotic response, and identified numerous novel associations for variants within these genes. Additional support was also provided for the implication of GxE in antipsychotic response, and many novel GxE were identified, emphasising the importance of considering childhood trauma in these types of studies. The tendency of childhood trauma to modify directionality of variant effects and alter overall patterns of significant associations was also demonstrated. This suggests that not accounting for the effects of childhood trauma may contribute toward some of the inconsistencies observed among the literature. This should be kept in mind for future studies of antipsychotic response, including large-scale hypothesis-free studies, as relevant confounders and modifiers are essential to consider in order to increase the biological validity of results.

Aside from the significant findings for antipsychotic response with variants and GxE with childhood trauma, no results from any of the other association analyses survived correction for multiple testing. In the case of antipsychotic response, it is possible that longitudinal treatment response data may allow for the detection of more subtle or relative differences in response over time between individuals (Schober and Vetter, 2018), thereby increasing power to find associations in smaller cohorts. However, this may only be the case when the predictors are categorical, i.e. variants, for which there are clearly defined genotypes. The opposite may be true for predictors that are continuous in nature and have minimal range in values, such as the variation in ROI volumes between individuals. Here, categorical outcome variables demonstrating phenotypic extremes (i.e. responders vs non-responders) may be preferable over the treatment trajectories derived from longitudinal response data, for the identification of significant associations in smaller cohorts. Of course, this may not apply in studies with large sample sizes where the statistical power can overcome complications relating to phenotypic nuances. However, for the innumerable research groups around the globe where limited sample sizes remain the only current option, these observations emphasise the importance of study design, and careful selection and definitions of phenotypes for investigating complex heterogeneous traits.

Despite the lack of statistical significance for findings relating to ROI volumes, the trend-level associations allowed the tentative exploration of relationships. This led to the identification of consistent trends between ROI volumes and antipsychotic response in the context of GxE with childhood trauma. Important to note here is the lack of consistency in the directionality of effects that was observed between ROI volumes and

antipsychotic response when only genetic variants were factored in. In other words, these findings suggest that the relationship between ROI volumes and antipsychotic response may be mediated through GxE with childhood trauma and variants conferring vulnerability or resilience to stress. Specifically, from these findings and from existing literature, it appears that severe experiences of childhood trauma may act as an insult to the developing brain, and that the extent of damage could be modulated by genotype in variants involved in neurodevelopment, neurotransmission, and synaptic plasticity (i.e. variants in *CACNA1C*, *COMT*, *DISC1*, *DRD3*, *NRG1*, and *OXTR*). Resulting reductions in brain volume could impair brain function, leading to deficits in the mechanisms involved in achieving responsiveness to antipsychotics. However, extensive research is required to support this hypothesis, and it is important to note that this is one of many processes potentially involved in a very complex system of underlying mechanisms contributing to antipsychotic treatment response.

All of the novel findings and trends identified in this study suggest that aside from increasing sample sizes as much as possible (as with the movement toward large-scale collaborative consortia), perhaps more effectively combining and assessing data may assist in revealing biologically relevant trends, even in smaller cohorts. However, considering the complexity and heterogeneity of antipsychotic response, clinically homogeneous cohorts are of the utmost importance here. Overall, this study identified promising new approaches and avenues to explore with respect to identifying underlying mechanisms of antipsychotic response, and provides support for a movement toward a more unified view of treatment outcome in schizophrenia.

5.2. Limitations

The greatest limitation of this study was the incomplete data for the cohort, as only 55 of the 103 participants had complete data for all variables, i.e. antipsychotic response (PANSS scores), genetics (variant genotypes), childhood trauma (CTQ scores), and brain structure (volumetric ROI measures). All 103 participants had treatment response and genotypic data, 75 participants had CTQ scores available, and 74 participants had structural MRI data. The sample sizes were therefore inconsistent among the various different association analyses, which hindered the reliability of cross-analysis comparisons and restricted the statistical power for several analyses, especially those incorporating both CTQ and MRI data (N = 55). Large, clinically homogeneous cohorts are necessary to achieve the power required to detect true associations in complex disorders and traits such as antipsychotic response. Novel trends reported in this study should therefore be considered as preliminary findings, which require validation in larger cohorts and other population groups. That said, the cohort in this study, albeit limited in size, was extremely well-characterised and homogenised. All participants were first-episode and treatment-naïve at the start of the study, and received the same long-acting injectable antipsychotic thereby ensuring adherence. Confounders such as illness course, treatment duration, differences in drugs, and non-adherence to treatment were therefore eliminated. This is important to note, as smaller cohorts of well-characterised patients will have the same power as larger cohorts of less well-characterised patients (Samuels et al., 2009). Additionally, cohorts of first-episode patients have increased power in pharmacogenetic studies (Zhang and Malhotra, 2013). This was demonstrated by the emergence of numerous novel significant findings surviving multiple testing in the genetic and GxE analyses of antipsychotic response.

The limitations of linear regression models should be recognised here, as the PANSS scores had to be log-transformed to satisfy the model assumptions. Whilst log-transforming the outcome variable to circumvent violations of model assumptions is commonly employed in linear regression analyses, most model diagnostics are based on visual assessments and can therefore be subjective. As overfitting of data can drastically impair the reliability of results, nonparametric statistical models would be more suitable to analyse data of this nature and would better capture the variance of PANSS scores (Lever et al., 2016). In terms of the effect sizes presented for the genetic associations with antipsychotic response, these were raw effect estimates conveying the differences in log-transformed PANSS scores between the different genotypes or number of minor alleles multiplied by time. In order to meaningfully interpret the effect of a specific variant, these effect estimates need to be back-transformed and expressed as a percentage change in PANSS scores over time. As the effect estimates for antipsychotic response were very small in this study, and as interpretations of these effects become further complicated with the incorporation of interaction terms (i.e. CTQ scores), emphasis was not placed on effect sizes but rather on direction of response for the sake of this exploratory analysis. Furthermore, the focus of this study was not on specific variants and their effects but rather on the comparison of trends across various analyses in order to assess the relationships between numerous variables in the context of antipsychotic response. Emphasis was therefore placed on directionality of effects across all analyses to simplify cross-analysis comparisons and provide a simplified overview of relationships between variables, in an exploratory manner. Future studies of this nature with larger cohorts and increased statistical power should focus more on specific effect sizes to reveal the most biologically relevant variants and pathways for further investigation including functional studies. That said, the results presented here may still prove useful in meta-analyses in the future.

Considering the neuroimaging aspects of this study, fMRI and DTI correlates of antipsychotic response were not explored, as only structural MRI data was available for the cohort. Furthermore, ROI volume was selected as the structural measurement of choice to investigate, as 1) the majority of previous structural imaging correlates of antipsychotic response were for ROI volumes, and 2) there was an abundance of volumetric measurements available in the data compared to other measurements such as thickness. However, it has been suggested that for genetic studies, cortical thickness and surface area measurements may be advantageous over volumetric measurements for gene discovery (Winkler et al., 2010). Although brain volume is heritable, volumetric measurements combine aspects of thickness and surface area which have been reported to be genetically uncorrelated (Winkler et al., 2010). Using volumetric measurements could therefore reduce sensitivity for detecting genetic correlates of brain structure by not discriminating the genetically distinct traits that are thickness and surface area (Winkler et al., 2010). In addition to this, only the total volumes were considered for the ROIs included in this study. This may have hindered the identification of associations relating to ROI volumes, as numerous imaging studies have reported unilateral ROI associations, thereby demonstrating differences in associations between left and right ROI volumes (Birur et al., 2017; Shenton et al., 2001; Wheeler and Voineskos, 2014).

In terms of the specific genes highlighted in this study, both *COMT* and *OXTR* have displayed sexually dimorphic effects in brain structure and psychiatric disorders (Carter, 2007; Harrison and Tunbridge, 2008; Wang et al., 2017). However, although all models were adjusted for sex, the cohort was not stratified by sex in order to perform separate analyses for these genes due to the small sample size. This phenomenon should

therefore be explored further in future studies where sample size allows, in case any associations were overlooked in our study. Another relevant modifier of genetic associations that was not explored in this study is epistasis. Gene-gene interactions have been found between several of the candidate genes in this study, in previous studies of both brain structure and antipsychotic response (Blasi et al., 2011; Montag et al., 2010; Takahashi et al., 2008; Tan et al., 2008; Tan et al., 2012). This needs to be taken into account when interpreting the results in this study, especially results involving the specific genes for which previous cases of epistasis have been identified, namely various combinations of *AKT1*, *BDNF*, *COMT*, *DRD2*, and *DRD3* (Blasi et al., 2011; Montag et al., 2010; Takahashi et al., 2008; Tan et al., 2008; Tan et al., 2012).

Childhood trauma was the only environmental factor that was explored in this study, yet importantly there are many other unknown environmental factors that could contribute to differential treatment outcomes via interactions with genes. Although environmental correlates of therapeutic response in schizophrenia are not well researched or characterised, other environmental contributors to psychosis may be important to investigate here, such as low socioeconomic status, urbanicity, and substance abuse (Misiak et al., 2017). Considering childhood trauma specifically, a further limitation would be that measures of positive environmental factors (i.e. social support) were not considered, which may mitigate the effects of childhood trauma thereby influencing treatment outcomes (Huot et al., 2004; Kaufman et al., 2000; van Winkel et al., 2014). Furthermore, as the CTQ is a self-report instrument, this assessment is subject to recall bias. This needs to be taken into account when interpreting results, which should also be validated in replication cohorts. However, it has been shown that the relationship between CTQ and clinical outcomes is not moderated by bias, as measured by the minimisation/ denial scale (MacDonald et al., 2015). In the context of GxE analyses, an assumption of these analyses is that genetic and environmental factors are independent of one another. However, gene-environment correlations can confound the detection of true GxE (Jaffee and Price, 2007), which was not controlled for in this study. Furthermore, to ensure observed effects are due to the GxE and not just one component of the interaction, all terms (G, E, GxE) should be included in the models (Mufford et al., 2017), which was not done in this study. That said, this study included separate analyses for “G”, “E”, and “GxE” for all outcomes allowing comparison of results, which could possibly circumvent this limitation.

5.3. Future prospects

The approach used in this study, along with the novel associations and trends identified, opens up a number of avenues to explore in future studies. Novel significant associations with treatment response point to variants and pathways of biological relevance for further exploration. Moreover, the novel significant GxE highlight the importance of environmental influences of treatment outcome and warrant further investigation of stress-response systems in relation to antipsychotic efficacy. Lastly, the relevance of considering a more unified view of treatment outcome was highlighted, along with the utility of more integrative research approaches. This provides a starting point for future studies of this nature, opening doors for the consideration of a multitude of factors and correlates to consider for further investigations of treatment response.

With this in mind, the findings from this study firstly require validation in independent cohorts, including those of other population groups, and importantly those of larger sample sizes. Not only is there a need for large collaborative consortia, such as the Psychiatric Genomics Consortium (PGC) and ENIGMA, to extend their

focus from schizophrenia aetiology to antipsychotic response, but also for large-scale hypothesis-free studies of antipsychotic response to incorporate environmental factors such as childhood trauma, given the propensity of childhood trauma to modify genetic associations.

Secondly, these findings should be explored in functional studies. The predicted roles of variants significantly associated with antipsychotic response were determined with the use of *in silico* prediction tools. The potential functional or regulatory impacts of these variants therefore require *in vitro* or *in vivo* validation. This will provide further biological insight with respect to the involvement of specific variants or pathways in functional systems, with the aim of progressing toward the discovery of clinically actionable biomarkers of antipsychotic response. In addition to this, the variants found to significantly modulate the effects of childhood trauma on antipsychotic response should be investigated for their potential role in stress vulnerability or resilience, in functional systems. The field of translational psychiatry is rapidly progressing, allowing the exploration of numerous experimental models for functional validation studies. These approaches include the use of animal models, and induced pluripotent stem cells (iPSCs) for the engineering of patient-derived neuronal cell lines. Aside from these, an exciting new technology for the *in vitro* investigation of neurodevelopmental processes and brain disorders is that of engineered brain microenvironments (Tate and Munson, 2019). These include brain organoids which are produced using three-dimensional cell culture techniques (Koo et al., 2019; Tate and Munson, 2019; Wang et al., 2017). It has been suggested that brain organoids could be used as a representative model system for the study of the human brain based on recent studies that demonstrated the ability of brain organoids to emulate the spatiotemporal dynamicity of neurogenesis, the formation of regional neural circuitry, and the integration of glial cells into a neural network (Koo et al., 2019). Engineered brain microenvironments can allow for the patient-specific exploration of characteristics of the brain, as well as direct examination of drug efficacy (Tate and Munson, 2019). Although in its infancy, this technology holds immense potential for the acceleration of research pertaining to personalised medicine in psychiatry.

Although there was a lack of power to identify significant associations across all analyses in this study, the approach may be valuable to implement in larger cohorts to assess whether similar trends are identified. Furthermore, this approach is transferrable to other complex multifactorial psychiatric disorders of uncharacterised aetiology. Using more integrative approaches where multiple correlates are investigated in a comparative fashion may accelerate the progress toward identifying underlying mechanisms of disorder aetiology and treatment response, which will assist in the long-term with more accurate diagnosis, implementations of more personalised treatment strategies, and development of novel therapies. However, in smaller cohorts this may only identify preliminary trends of interest for further investigation, as in this study.

Considering only the correlates included in this study (genetics, neuroimaging, and childhood trauma), there are several options for variable approaches in future studies. For example, in addition to genetic variants, one could consider haploblocks in candidate genes, and polygenic risk scores (PRS) could also be generated for schizophrenia cohorts using the PGC schizophrenia summary statistics. PRS and haplotypes could then be investigated for associations with antipsychotic response and ROI volumes, with and without interaction with childhood trauma. Furthermore, studies could incorporate various neuroimaging measurements besides ROI volumes, such as fMRI or DTI measures. The relationships between these measurements would also be of interest to evaluate, for example relating brain structure to function in the context of GxE and antipsychotic

response. This type of approach could also be expanded to consider additional potential correlates of antipsychotic response. For example, as GxE are said to be mediated by epigenetic mechanisms, epigenetic factors such as DNA methylation would be important and relevant to consider in this context. Furthermore, gene-gene interactions, and GxE with other environmental contributors such as substance abuse, could be explored. Moving forward, multi-omics approaches should also be embraced, combining genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles; the integrative personal omics profile (iPOP) is an example of this (Chen et al., 2012). However, it should be kept in mind that the more variables included in a study, the greater the statistical power required for analyses. Furthermore, statistical approaches will need to be carefully selected in order to conduct the most appropriate and accurate analyses for specific combinations of variables. This is an important consideration for future studies of this nature, as statistics and biology have become inextricably linked. As an example, linear regression models sometimes recommend the rescaling of predictors with vastly different scales. Additionally, various transformations of data may be necessary to satisfy the model assumptions, as demonstrated in this study. Therefore, increases in the numbers of variables included may increase the amount of data manipulation necessary for analyses with specific models. This may decrease the accuracy and reliability of results, and may not be the best way to capture the variance of certain variables. With this in mind, a number of different multivariate approaches can be explored in future studies, each with their own advantages and limitations. These include methods such as independent component analysis (ICA), canonical correlation analysis, sparse partial least squares, and sparse reduced-rank regression (Mufford et al., 2017). In addition to these methods, machine learning approaches and dimensionality reduction techniques can also be employed, among many others (Bzdok and Meyer-Lindenberg, 2018; Durstewitz et al., 2019; Misra et al., 2019; Zeng and Lumley, 2018). This in itself presents an opportunity for a multitude of studies, as the advancement and comparison of statistical approaches for the reliable analysis of large, mixed datasets is essential for the progress toward personalised medicine approaches in psychiatry.

Overall, this study identified a number of significant findings and exploratory trends of interest for future consideration. The significant associations between genetic variants and antipsychotic treatment response lend evidence to the involvement of a number of candidate genes in differential treatment outcomes, whilst contributing novel variants within these genes. Considering all of the different analyses in this study, the vast majority of significant findings were for GxE of antipsychotic treatment response. In addition to providing support for the involvement of GxE in treatment response, these findings highlighted the propensity of childhood trauma to modify both effect directionality and overall patterns of genetic associations with treatment response. Not only does this emphasise the importance of including childhood trauma in genetic studies of antipsychotic response, but also the relevance of considering additional environmental modifiers in future studies. Lastly, with respect to the imaging genetics and iGxE aspects of the study, despite the insufficient power to detect significant associations with ROI volumes, an intriguing trend was observed for the iGxE of antipsychotic treatment response. Here, for GxE conferring significantly poorer treatment response, trend-level reductions in several ROI volumes were observed, and vice versa, highlighting a positive correlation between ROI volumes and treatment response in the context of specific GxE. These findings present numerous options for future studies, and suggest that integrative research approaches may more effectively disentangle underlying mechanisms of complex phenotypes such as treatment response, if implemented in well-powered and well-characterised cohorts.

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APPENDIX A

Supplementary data

Table S1. RegulomeDB scoring system (Boyle et al., 2012).

Category	Description
	Likely to affect binding and linked to expression of a gene target
1a	eQTL + TF binding + matched TF motif + matched DNase footprint + DNase peak
1b	eQTL + TF binding + any motif + DNase footprint + DNase peak
1c	eQTL + TF binding + matched TF motif + DNase peak
1d	eQTL + TF binding + any motif + DNase peak
1e	eQTL + TF binding + matched TF motif
1f	eQTL + TF binding/ DNase peak
	Likely to affect binding
2a	TF binding + matched TF motif + matched DNase footprint + DNase peak
2b	TF binding + any motif + DNase footprint + DNase peak
2c	TF binding + matched TF motif + DNase peak
	Less likely to affect binding
3a	TF binding + any motif + DNase peak
3b	TF binding + matched TF motif
	Minimal binding evidence
4	TF binding + DNase peak
5	TF binding or DNase peak
6	Motif hit

Category 1 is the most significant and category 6 is the least significant with respect to regulatory effects.

Table S2. List of all volumetric measures of brain structure implicated in antipsychotic treatment response, as reported in the respective studies.

Number	Volumetric measure	Reference/s
1	**Caudate**	(Hutcheson et al., 2014; Molina et al., 2011)
2	Corpus callosum	(Nakajima et al., 2015)
3	**Cortex**	(Zipursky et al., 1998)
4	Cortical sulcus	(Honer et al., 1995)
5	Dorsolateral prefrontal cortex	(Nakajima et al., 2015)
6	**Grey matter**	(Altamura et al., 2017)
7	**Hippocampal tail**	(Bodnar et al., 2010)
8	**Hippocampus**	(Nakajima et al., 2015; Savas et al., 2002)
9	Insula	(Molina et al., 2011)
10	Intracranium	(Nakajima et al., 2015)
11	Middle frontal gyrus	(Quarantelli et al., 2014)
12	Orbital grey matter	(Molina et al., 2004)
13	**Pallidum**	(Hutcheson et al., 2014)
14	Parahippocampal cortex	(Bodnar et al., 2012)
15	Parahippocampal gyrus	(Bodnar et al., 2010)
16	Pituitary	(Garner et al., 2009)
17	Prefrontal cortex	(Nakajima et al., 2015)
18	Prefrontal grey matter	(Nakajima et al., 2015)
19	**Putamen**	(Buchsbaum et al., 2003; Hutcheson et al., 2014; Mitelman et al., 2009; Molina et al., 2011)
20	Rectal gyrus	(Molina et al., 2011)
21	Splenium	(Nakajima et al., 2015)
22	**Subcortical regions: frontal***	(Molina et al., 2010)
23	**Subcortical regions: limbic cortices***	(Molina et al., 2010)
24	**Subcortical regions: occipital***	(Molina et al., 2010)
25	Superior gyrus	(Quarantelli et al., 2014)
26	Temporal grey matter	(Nakajima et al., 2015)

Measures identified in the available structural MRI data are highlighted in red and in bold.
*These specific subcortical regions were not present in the available structural MRI data, so the available measure of "subcortical grey matter" was selected as a proxy for inclusion in the study.

Table S3. Lists of genes implicated in antipsychotic treatment response and brain structure, identified via a search of literature and the NHGRI-EBI GWAS Catalog.

Number	Brain structure	Antipsychotic response
1	***AKT1***	*5-HT1A*
2	*ANK3*	*5-HT2A*
3	*APOE*	*5-HT2C*
4	*APOOP3*	*5-HT3A*
5	*ARL6IP1P3*	*5-HT6*
6	*ASCC3*	*5-HTT*
7	*ASTN2*	*AC009562.1*
8	*ASTN2*	*AC025281.1*
9	*ATP7BP1*	*AC026320.2*
10	*BCL2L1*	*AC093913.1*
11	*BCL2L1*	*ADR1A*
12	***BDNF***	*AJAP1*
13	*C1orf168*	***AKT1***
14	***CACNA1C***	*AL162391.1*
15	*CCKAR*	*AL589923.1*
16	*CLU*	*ANKK1*
17	*CNNM2*	*ANKS1B*
18	***CNR1***	*AP006295.1*
19	***COMT***	*ARID5B*
20	*CRHR1*	*ATP1A2*
21	*DCC*	*ATP2B2*
22	*DCC*	*BAG3*
23	*DDR2*	***BDNF***
24	*DENND4B*	***CACNA1C***
25	***DISC1***	***CNR1***
26	*DLG2*	*CNTN4*
27	*DLG2*	*CNTNAP5*
28	*DPP4*	***COMT***
29	*DPP4*	*CRCT1*
30	***DRD2***	*CYP2C19*
31	***DRD3***	*CYP2D6*
32	*DSCAML1*	*DAT*
33	***DTNBP1***	***DISC1***
34	*DYNC1I2*	*DRD1*
35	*EIF4G3*	***DRD2***
36	*EPB41L2*	***DRD3***
37	*FAM19A2*	***DTNBP1***
38	*FAM86B3P*	*EDN1*
39	*FAT3*	*EIF2AK4*
40	*FOXO3*	*EPHA6*
41	*G72*	*GFRA2*
42	*GATAD2B*	*GNB3*
43	*GRID1*	*GRIA4*
44	*GRIN2A*	*GRIN2B*
45	*GSK3β*	*GRM3*
46	*HEATR4*	*GRM7*
47	*HELZ*	*HCG20*
48	*HMGA2*	*HIVEP1*

49	*HOXC4*	*HS3ST2*
50	*HOXC5*	*HTR2A*
51	*HRK*	*HTR3B*
52	*HS3ST5*	*IGSF8*
53	*IL-1b*	***IL-1RN***
54	***IL-1RN***	*KCNH2*
55	*ITIH4*	*KCNH5*
56	*KANSL1*	*LCE3E*
57	*KRT18P32*	*MC2R*
58	*KTN1*	*MCP-1*
59	*LEMD3*	*MDR1*
60	*LOC101927768*	*MEGF10*
61	*LOC101929199*	*MTHFR*
62	*LOC101929446*	*MTRR*
63	*LOC102723803*	*MYO7B*
64	*LOC105369409*	*NEF3*
65	*LOC105369860*	*NPAS3*
66	*LOC105369914*	*NR3C2*
67	*LOC105370284*	***NRG1***
68	*LOC105370285*	*OXT*
69	*LOC105370802*	***OXTR***
70	*LOC105371448*	*PAICS*
71	*LOC105371611*	*PCDH7*
72	*LOC105372698*	*PDE4D*
73	*LOC105373592*	*PDE7B*
74	*LOC105374004*	*PIP5K1B*
75	*LOC105374007*	*PPA2*
76	*LOC105375199*	*PTGFRN*
77	*LOC105375951*	*RF00019*
78	*LOC105375976*	*RF01210*
79	*LOC105378986*	***RGS4***
80	*LOC107984373*	*RNA5SP428*
81	*LOC107984425*	*RNU6-544P*
82	*LOC284395*	*RPL17P44*
83	*LOC387820*	*RTKN2*
84	*LOC400794*	*SLC1A1*
85	*MAP2*	*SLC6A2*
86	*MAST4*	*SPOPL*
87	*MCTP2*	*ST6GAL2*
88	*MEAF6P1*	*TJP1*
89	*MGC57346-CRHR1*	***TNF-a***
90	*MIPEPP2*	*TNFRSF11A*
91	*MIR137HG*	*TNIK*
92	*MIR492*	*TNR*
93	*MRPL11P3*	*TRPM1*
94	*MSRB3*	*UNC5C*
95	*NCAN*	*XKR4*
96	*NOTCH4*	*ZBTB20*
97	***NRG1***	***ZNF804A***
98	*NRGN*	
99	*NTF3*	

100	***OXTR***
101	*PARD3B*
102	*PCDH12*
103	*PCM1*
104	*PICALM*
105	*PIK3C2G*
106	*PRELID1P1*
107	*PRODH*
108	*RAB3C*
109	*RAPGEF4*
110	*RASGRF2*
111	*RELN*
112	***RGS4***
113	*RN7SL340P*
114	*RPL13AP3*
115	*RPL36P15*
116	*RPL7AP4*
117	*RPS4XP18*
118	*SGK223*
119	*SLC39A1*
120	*SLC4A10*
121	*SNTG1*
122	*SPATS2L*
123	*STIM2*
124	*TBC1D19*
125	*TBPL2*
126	*TBXAS1*
127	*TCF4*
128	*TGFA*
129	*TGFA-IT1*
130	***TNF-a***
131	*TOMM40*
132	*WDR60*
133	*YAP1P3*
134	***ZNF804A***

Genes highlighted in blue were identified via the NHGRI-EBI GWAS Catalog.
Genes in white were identified in the literature.
ANKS1B (highlighted in purple) was found in the literature and in the NHGRI-EBI GWAS Catalog.
Genes highlighted in red and in bold were found in both gene lists, i.e. implicated in both brain structure and antipsychotic response, and were thus selected as candidate genes for this study. All of these genes were identified through the literature search only.

Table S4. Summary of general information and predicted functional impact of all prioritised variants.

Gene	Chr	SNP rsID	MAF	Ensembl			SNPnexus (GRCh38)		SIFT		Polyphen-2
				Position GRCh37	Alleles		Functional consequence	SIFT	Polyphen	Ortholog prediction	Homolog prediction	
					Anc	Alt						
BDNF	11	rs6265	0.1165	27679916	*C*	*T*	Missense/3' UTR/downstream/NMD target	Tolerated	Benign/probably damaging	Damaging (low confidence)	Damaging (low confidence)	Possibly damaging
BDNF	11	rs11030104	0.1408	27684517	*A*	*G*	Intronic/upstream/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
BDNF	11	rs10835210	0.2313	27695910	*C*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
BDNF	11	rs988748	0.2451	27724745	*G*	*C*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs11062040	0.4515	2091257	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2429127	0.2767	2116768	*T*	*C*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10161032	0.3447	2154103	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs765125	0.2794	2156207	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs11062093	0.1796	2166479	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs7297992	0.3922	2171649	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs6489348	0.4369	2208215	*C*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs4126711	0.4069	2227311	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2238034	0.1019	2235628	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10848635	0.3400	2316195	*A*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs1016388	0.3500	2321868	*T*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs11062162	0.4223	2332104	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2007044	0.3495	2344960	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs1006737	0.2864	2345295	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10848645	0.3107	2420244	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10774037	0.1796	2420526	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs3819536	0.2767	2436998	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2238070	0.3107	2456115	*G*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2239056	0.1408	2468195	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs740417	0.3689	2499849	*A*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10491964	0.1990	2500431	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2370515	0.1796	2511162	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs4765687	0.4709	2560116	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs4765937	0.3010	2570535	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2239084	0.1699	2577104	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs1015287	0.4806	2605386	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10848665	0.1068	2609084	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2238087	0.1019	2613716	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs11062260	0.1068	2646783	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs4394887	0.1699	2649980	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2239118	0.4461	2660753	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*

CACNA1C	12	rs1034936	0.4500	2661160	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs4765961	0.3155	2668472	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2370602	0.2282	2676683	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs215976	0.1505	2694638	*C*	*T*	Missense/synonymous	Tolerated	Possibly/probably damaging/benign	*ND*	*ND*	*ND*
CACNA1C	12	rs2238096	0.2961	2749913	*A*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs2302729	0.4175	2783972	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
CACNA1C	12	rs10848683	0.3932	2791130	*T*	*C*	Intronic	*ND*	*ND*	Tolerated	Damaging (low confidence)	Benign
CACNA1C	12	rs4765970	0.2598	2792661	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs9606186	0.3010	19920359	*G*	*C*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs2075507	0.2961	19928092	*A*	*G*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs2020917	0.2376	19928884	*C*	*T*	Intronic/upstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs737866	0.2476	19930109	*T*	*C*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs737865	0.2476	19930121	*A*	*G*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs933271	0.4175	19931407	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs174674	0.4133	19934025	*A*	*G*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs5993883	0.4660	19937638	*G*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs740603	0.4752	19945177	*G*	*A*	Intronic/upstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs165656	0.4356	19948863	*G*	*C*	Intronic/upstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs165722	0.4757	19949013	*C*	*T*	Intronic/upstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs6269	0.3252	19949952	*G*	*A*	TF binding site/Intronic/5' UTR/upstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs4633	0.3932	19950235	*C*	*T*	Synonymous/upstream/NMD target/nctarnscript exonic	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs2239393	0.3687	19950428	*A*	*G*	Intronic/upstream/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs4818	0.2780	19951207	*G*	*C/T*	Synonymous/upstream/downstream/NMD target/noncoding transcript exonic	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs4680	0.3592	19951271	*G*	*A*	Missense/upstream/downstream/NMD target	Tolerated/deleterious	Benign	Damaging	Tolerated	Benign
COMT	22	rs174697	0.1262	19953832	*G*	*A*	Intronic/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*

COMT	22	rs165599	0.3824	19956781	*G*	*A*	Downstream/3' UTR	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs165728	0.1456	19957023	*T*	*C*	Downstream/3' UTR	*ND*	*ND*	*ND*	*ND*	*ND*
COMT	22	rs9265	0.3950	19957631	*C*	*A*	Downstream/3' UTR	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs1417584	0.4903	231819050	*C*	*T*	Intronic/upstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs2487453	0.4951	231863204	*T*	*C*	Intronic/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs4658883	0.1845	231876767	*T*	*C*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs12066910	0.3056	231881732	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs10864695	0.2767	231885217	*A*	*G*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs2492367	0.1699	231906589	*C*	*T*	Missense/synonymous/intronic/NMD target/3'UTR	Deleterious /tolerated	Possibly/probably damaging/benign	*ND*	*ND*	*ND*
DISC1	1	rs2812391	0.2767	231911976	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs16854954	0.2961	231912592	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs17766087	0.1359	231917877	*T*	*G*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs9803690	0.3883	231923345	*G*	*A*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs1322784	0.4951	231928935	*G*	*A*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs2255340	0.4608	231936150	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs2738875	0.1602	231945373	*G*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs6675281	0.1165	231954101	*C*	*T*	Missense/synonymous/upstream/downstream/intronic/NMD target/3'UTR	Deleterious	Possibly/probably damaging	Damaging	Damaging	Probably damaging
DISC1	1	rs1535530	0.3835	231954427	*T*	*C*	Intronic/NMD target/3' UTR/upstream/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs1000730	0.3835	231963601	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs7552697	0.1893	231997560	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs12757857	0.3932	231998863	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs3082	0.2282	232002392	*A*	*G*	Intronic/NMD target/3' UTR	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs1407601	0.1748	232003412	*G*	*T*	Intronic/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs2356606	0.2184	232015040	*A*	*G*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs4658889	0.2670	232019810	*G*	*A*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs9431714	0.2913	232021248	*G*	*A*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs821722	0.4951	232036030	*A*	*G*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*

DISC1	1	rs7541019	0.1436	232051185	*T*	*G*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs11584798	0.1359	232066277	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs701158	0.2476	232073128	*G*	*A*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs701160	0.4175	232092481	*T*	*C*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs821615	0.2573	232143946	*C*	*T*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs821616	0.2621	232144598	*A*	*T*	Missense/3' UTR/NMD target	Deleterious	Possibly/probably damaging	Tolerated	Damaging	Probably damaging
DISC1	1	rs821631	0.3204	232148135	*C*	*T*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs821639	0.3447	232149843	*A*	*G*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs9729194	0.3689	232168867	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs11122396	0.2282	232175268	*G*	*A*	3' UTR	*ND*	*ND*	*ND*	*ND*	*ND*
DISC1	1	rs16856322	0.2816	232176987	*C*	*T*	3' UTR/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs1800497	0.3186	113270828	*A*	*G*	Missense/downstream	Tolerated	Benign	Tolerated	Tolerated	Benign
DRD2	11	rs6278	0.1359	113280724	*C*	*A*	3' UTR/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs6277	0.1632	113283459	*G*	*A*	Synonymous/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs6275	0.4069	113283477	*G*	*A*	Synonymous/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs1076560	0.1689	113283688	*C*	*A*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs12363125	0.2282	113285916	*T*	*C*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs1800498	0.2732	113291588	*G*	*A*	Intronic/upstream/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs1079597	0.1942	113296286	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs2471857	0.2816	113298339	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs4436578	0.4126	113306765	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs4245146	0.4029	113317973	*T*	*C*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs7131056	0.4559	113329774	*C*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs4630328	0.1505	113334209	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs1799978	0.1699	113346351	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD2	11	rs2514218	0.1942	113392994	*C*	*T*	Intergenic	*ND*	*ND*	*ND*	*ND*	*ND*
DRD3	3	rs167771	0.3981	113876275	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
DRD3	3	rs6280	0.3835	113890815	*C*	*T*	Missense	Tolerated (low confidence)	Benign	Tolerated	Tolerated	Benign
DRD3	3	rs9825563	0.4806	113900220	*G*	*A*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
DRD3	3	rs1394016	0.2913	113909889	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
DTNBP1	6	rs1047631	0.1990	15523101	*T*	*C*	3' UTR/upstream/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*

DTNBP1	6	rs4712253	0.4369	15526417	*C*	*T*	Intronic/upstream/downstream/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DTNBP1	6	rs2619522	0.4272	15653649	*C*	*A*	Intronic/NMD target	*ND*	*ND*	*ND*	*ND*	*ND*
DTNBP1	6	rs2619536	0.1796	15663847	*T*	*C*	Upstream	*ND*	*ND*	*ND*	*ND*	*ND*
IL1RN	2	rs315920	0.1019	113873018	*C*	*T*	Intronic/upstream	*ND*	*ND*	*ND*	*ND*	*ND*
IL1RN	2	rs423904	0.1386	113887262	*C*	*T*	Intronic/noncoding transcript exonic	*ND*	*ND*	*ND*	*ND*	*ND*
IL1RN	2	rs3087266	0.3155	113889100	*T*	*C*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
IL1RN	2	rs315952	0.4272	113890304	*C*	*T*	Missense/synonymous/downstream	Tolerated	Possibly damaging/benign	*ND*	*ND*	*ND*
NRG1	8	rs35753505	0.1553	31474141	*T*	*C*	Intergenic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs6994992	0.3592	31495581	*C*	*T*	Upstream	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs28401439	0.1845	31496006	*G*	*T*	Upstream	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs6987996	0.4417	31506771	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs4733094	0.1311	31597593	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs16878394	0.1893	31727061	*G*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs796549	0.2670	31768217	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs7002063	0.3252	31803534	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2010243	0.4903	31846380	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs1462900	0.1845	31927638	*A*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs1381874	0.2524	31942557	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs7841220	0.3155	31943664	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs10503899	0.2039	31947234	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs11776959	0.2476	31948864	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs10503901	0.3786	32085171	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs1481728	0.2767	32116927	*T*	*G*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs4733313	0.4466	32118416	*C*	*T*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs900102	0.4223	32120188	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs16879067	0.1650	32121424	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs17624592	0.1408	32122424	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs11778887	0.1942	32156724	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs7005124	0.2282	32167730	*G*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs1685117	0.1942	32197182	*G*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs7841599	0.4653	32199572	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs970998	0.3689	32201084	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs1565031	0.1505	32201135	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs1623372	0.3350	32215602	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs16879304	0.1408	32240840	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs939077	0.2913	32245538	*G*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs4733325	0.3835	32247220	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs3847131	0.4223	32282019	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs9297192	0.1117	32283517	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs17716295	0.1650	32317917	*C*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*

NRG1	8	rs12216802	0.1214	32340967	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs17645417	0.4069	32351333	*T*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs7844425	0.1505	32375617	*T*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs4733347	0.1765	32376010	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs4733130	0.2379	32406994	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2439312	0.1699	32412359	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs17721043	0.1505	32436875	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2439292	0.3204	32446882	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs3924999	0.1990	32453358	*G*	*A*	Missense	Deleterious /tolerated	Benign/possibly damaging	Tolerated	Tolerated	Possibly damaging
NRG1	8	rs2919370	0.3155	32476816	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2466049	0.1262	32514916	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2919392	0.4320	32524451	*A*	*G*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2919390	0.4806	32526955	*C*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs2976532	0.1845	32594251	*G*	*A*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
NRG1	8	rs73672607	0.1520	32621805	*C*	*A*	Missense/downstream/ 3' UTR	Deleterious	Probably/possib ly damaging	Damaging	Damaging (low confidence)	*ND*
OXTR	3	rs237884	0.4563	8793585	*G*	*A*	Intronic/3' UTR	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs237885	0.4608	8795543	*G*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs11706648	0.2282	8796547	*A*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs237888	0.2718	8797095	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs4686301	0.1942	8798586	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs237889	0.1845	8802483	*C*	*T*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs2268495	0.2621	8807535	*A*	*G*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs237899	0.2767	8808515	*G*	*A*	Intronic/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
OXTR	3	rs4686302	0.1350	8809222	*C*	*T*	Missense/intronic/down stream	Tolerated	Benign	Tolerated	Tolerated	Benign
RGS4	1	rs951439	0.4660	163033691	*C*	*T*	upstream	*ND*	*ND*	*ND*	*ND*	*ND*
RGS4	1	rs2661319	0.2864	163039777	*T*	*C*	Intronic/upstream/regul atory	*ND*	*ND*	*ND*	*ND*	*ND*
RGS4	1	rs10759	0.2039	163046351	*T*	*G*	3' UTR/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
TNF-α	6	rs1800629	0.1262	31543031	*G*	*A*	Upstream/downstream	*ND*	*ND*	*ND*	*ND*	*ND*
TNF-α	6	rs1800630	0.1042	31542476	*C*	*A*	Downstream	*ND*	*ND*	*ND*	*ND*	*ND*
ZNF804A	2	rs1344706	0.1748	185778428	*A*	*C*	Intronic	*ND*	*ND*	*ND*	*ND*	*ND*
ZNF804A	2	rs12476147	0.4709	185800905	*T*	*A*	Missense	*ND*	*ND*	Tolerated	Tolerated	Benign
ZNF804A	2	rs4667001	0.2816	185801747	*G*	*A*	Missense	Tolerated	Benign	Tolerated	Tolerated	Benign
ZNF804A	2	rs1366842	0.2816	185802243	*C*	*A*	Missense	Tolerated	Benign	Tolerated	Tolerated	Benign
ZNF804A	2	rs12477430	0.3447	185802363	*G*	*A*	Missense	Tolerated	Benign	Tolerated	Tolerated	Benign

Chr = Chromosome; MAF = Minor allele frequency in the study cohort, obtained via PLINK v1.9; Anc = Ancestral allele; Alt = Alternate allele; NMD = Nonsense-mediated mRNA decay; *ND* = Not determined.

Results coloured in blue fulfilled the defined criteria for prioritisation.

Table S5. Summary of prioritised variants showing previously reported associations with brain structure and antipsychotic treatment response.

Gene	SNP rsID	Literature	NGHRI-EBI GWAS Catalog	PharmGKB	
				Clinical annotations	Variant annotations
BDNF	rs6265	Yes (both)	No	AP efficacy/toxicity	AP response/ADRs
BDNF	rs11030104	Yes (AP response)	No	AP efficacy	AP response
BDNF	rs10835210	No	No	No	No
BDNF	rs988748	No	No	No	No
CACNA1C	rs11062040	No	No	No	No
CACNA1C	rs2429127	No	No	No	No
CACNA1C	rs10161032	No	No	No	No
CACNA1C	rs765125	No	No	No	No
CACNA1C	rs11062093	No	No	No	No
CACNA1C	rs7297992	No	No	No	No
CACNA1C	rs6489348	No	No	No	No
CACNA1C	rs4126711	No	No	No	No
CACNA1C	rs2238034	No	No	No	No
CACNA1C	rs10848635	Yes (AP response)	No	No	No
CACNA1C	rs1016388	Yes (AP response)	No	No	No
CACNA1C	rs11062162	No	No	No	No
CACNA1C	rs2007044	No	No	No	No
CACNA1C	rs1006737	Yes (both)	No	No	No
CACNA1C	rs10848645	No	No	No	No
CACNA1C	rs10774037	No	No	No	No
CACNA1C	rs3819536	No	No	No	No
CACNA1C	rs2238070	No	No	No	No
CACNA1C	rs2239056	No	No	No	No
CACNA1C	rs740417	No	No	No	No
CACNA1C	rs10491964	No	No	No	No
CACNA1C	rs2370515	No	No	No	No
CACNA1C	rs4765687	No	No	No	No
CACNA1C	rs4765937	No	No	No	No
CACNA1C	rs2239084	No	No	No	No
CACNA1C	rs1015287	No	No	No	No
CACNA1C	rs10848665	No	No	No	No
CACNA1C	rs2238087	Yes (AP response)	No	No	No
CACNA1C	rs11062260	No	No	No	No
CACNA1C	rs4394887	No	No	No	No
CACNA1C	rs2239118	No	No	No	No
CACNA1C	rs1034936	Yes (AP response)	No	No	No
CACNA1C	rs4765961	No	No	No	No
CACNA1C	rs2370602	No	No	No	No
CACNA1C	rs215976	No	No	No	No
CACNA1C	rs2238096	No	No	No	No
CACNA1C	rs2302729	No	No	No	No
CACNA1C	rs10848683	No	No	No	No
CACNA1C	rs4765970	No	No	No	No
COMT	rs9606186	No	No	AP response	AP response
COMT	rs2075507	Yes (brain structure)	No	No	No
COMT	rs2020917	No	No	No	AP response
COMT	rs737866	No	No	No	No
COMT	rs737865	Yes (AP response)	No	No	No
COMT	rs933271	No	No	No	AP response
COMT	rs174674	No	No	No	No
COMT	rs5993883	No	No	AP efficacy	AP response
COMT	rs740603	No	No	No	No
COMT	rs165656	No	No	No	No
COMT	rs165722	No	No	No	No
COMT	rs6269	Yes (AP response)	No	AP efficacy	AP response
COMT	rs4633	Yes (AP response)	No	No	AP response
COMT	rs2239393	No	No	No	No
COMT	rs4818	Yes (AP response)	No	AP efficacy	AP response
COMT	rs4680	Yes (both)	No	AP efficacy/toxicity	AP response/ADRs
COMT	rs174697	No	No	No	No
COMT	rs165599	No	No	AP efficacy	AP response
COMT	rs165728	No	No	No	No
COMT	rs9265	No	No	No	No

DISC1	rs1417584	No	No	No	No
DISC1	rs2487453	Yes (brain structure)	Brain structure	No	No
DISC1	rs4658883	No	No	No	No
DISC1	rs12066910	No	No	No	No
DISC1	rs10864695	No	No	No	No
DISC1	rs2492367	No	No	No	No
DISC1	rs2812391	No	No	No	No
DISC1	rs16854954	Yes (brain structure)	Brain structure	No	No
DISC1	rs17766087	No	No	No	No
DISC1	rs9803690	No	No	No	No
DISC1	rs1322784	No	No	No	No
DISC1	rs2255340	No	No	No	No
DISC1	rs2738875	No	No	No	No
DISC1	rs6675281	Yes (both)	No	No	No
DISC1	rs1535530	Yes (brain structure)	No	No	No
DISC1	rs1000730	No	No	No	No
DISC1	rs7552697	No	No	No	No
DISC1	rs12757857	No	No	No	No
DISC1	rs3082	No	No	No	No
DISC1	rs1407601	No	No	No	No
DISC1	rs2356606	Yes (brain structure)	Brain structure	No	No
DISC1	rs4658889	No	No	No	No
DISC1	rs9431714	Yes (brain structure)	Brain structure	No	No
DISC1	rs821722	No	No	No	No
DISC1	rs7541019	No	No	No	No
DISC1	rs11584798	No	No	No	No
DISC1	rs701158	No	No	No	No
DISC1	rs701160	No	No	No	No
DISC1	rs821615	No	No	No	No
DISC1	rs821616	Yes (brain structure)	No	No	No
DISC1	rs821631	No	No	No	No
DISC1	rs821639	Yes (brain structure)	Brain structure	No	No
DISC1	rs9729194	No	No	No	No
DISC1	rs11122396	No	No	No	No
DISC1	rs16856322	Yes (brain structure)	Brain structure	No	No
DRD2	rs1800497	Yes (both)	No	AP efficacy/toxicity	AP ADR
DRD2	rs6278	No	No	No	No
DRD2	rs6277	No	No	AP efficacy/toxicity	AP ADR
DRD2	rs6275	Yes (AP response)	No	AP prolactin	AP ADR and prolactin
DRD2	rs1076560	Yes (AP response)	No	AP efficacy	AP response
DRD2	rs12363125	No	No	No	No
DRD2	rs1800498	Yes (AP response)	No	No	No
DRD2	rs1079597	Yes (AP response)	No	AP efficacy	AP response
DRD2	rs2471857	No	No	No	No
DRD2	rs4436578	No	No	AP toxicity	AP ADR
DRD2	rs4245146	No	No	No	No
DRD2	rs7131056	No	No	No	AP ADR
DRD2	rs4630328	No	No	No	No
DRD2	rs1799978	Yes (AP response)	No	AP efficacy/toxicity	AP response
DRD2	rs2514218	Yes (AP response)	No	No	AP response
DRD3	rs167771	No	No	AP toxicity	AP response
DRD3	rs6280	Yes (both)	No	AP efficacy	AP response
DRD3	rs9825563	No	No	No	No
DRD3	rs1394016	No	No	No	No
DTNBP1	rs1047631	No	No	No	No
DTNBP1	rs4712253	No	No	No	No
DTNBP1	rs2619522	Yes (brain structure)	No	No	No
DTNBP1	rs2619536	No	No	No	No
IL1RN	rs315920	No	No	No	No
IL1RN	rs423904	No	No	No	No
IL1RN	rs3087266	No	No	No	No
IL1RN	rs315952	No	No	No	No
NRG1	rs35753505	Yes (both)	No	No	No
NRG1	rs6994992	Yes (brain structure)	No	No	No
NRG1	rs28401439	No	No	No	No
NRG1	rs6987996	No	No	No	No
NRG1	rs4733094	No	No	No	No
NRG1	rs16878394	No	No	No	No

NRG1	rs796549	No	No	No	No
NRG1	rs7002063	No	No	No	No
NRG1	rs2010243	No	No	No	No
NRG1	rs1462900	No	No	No	No
NRG1	rs1381874	No	No	No	No
NRG1	rs7841220	No	No	No	No
NRG1	rs10503899	No	No	No	No
NRG1	rs11776959	No	No	No	No
NRG1	rs10503901	No	No	No	No
NRG1	rs1481728	No	No	No	No
NRG1	rs4733313	No	No	No	No
NRG1	rs900102	No	No	No	No
NRG1	rs16879067	No	No	No	No
NRG1	rs17624592	No	No	No	No
NRG1	rs11778887	No	No	No	No
NRG1	rs7005124	No	No	No	No
NRG1	rs1685117	No	No	No	No
NRG1	rs7841599	No	No	No	No
NRG1	rs970998	No	No	No	No
NRG1	rs1565031	No	No	No	No
NRG1	rs1623372	No	No	No	No
NRG1	rs16879304	No	No	No	No
NRG1	rs939077	No	No	No	No
NRG1	rs4733325	No	No	No	No
NRG1	rs3847131	No	No	No	No
NRG1	rs9297192	No	No	No	No
NRG1	rs17716295	Yes (AP response)	No	AP efficacy	AP response
NRG1	rs12216802	No	No	No	No
NRG1	rs17645417	No	No	No	No
NRG1	rs7844425	No	No	No	No
NRG1	rs4733347	No	No	No	No
NRG1	rs4733130	No	No	No	No
NRG1	rs2439312	No	No	No	No
NRG1	rs17721043	No	No	No	No
NRG1	rs2439292	No	No	No	No
NRG1	rs3924999	No	No	No	No
NRG1	rs2919370	No	No	No	No
NRG1	rs2466049	No	No	No	No
NRG1	rs2919392	No	No	No	No
NRG1	rs2919390	No	No	No	No
NRG1	rs2976532	No	No	No	No
NRG1	rs73672607	No	No	No	No
OXTR	rs237884	No	No	No	No
OXTR	rs237885	No	No	No	No
OXTR	rs11706648	Yes (AP response)	No	No	No
OXTR	rs237888	No	No	No	No
OXTR	rs4686301	Yes (AP response)	No	No	No
OXTR	rs237889	No	No	No	No
OXTR	rs2268495	No	No	No	No
OXTR	rs237899	Yes (AP response)	No	No	No
OXTR	rs4686302	No	No	No	No
RGS4	rs951439	Yes (AP response)	No	AP efficacy	AP response
RGS4	rs2661319	Yes (both)	No	AP efficacy	AP response
RGS4	rs10759	Yes (AP response)	No	No	No
TNF-α	rs1800629	Yes (both)	No	No	No
TNF-α	rs1800630	No	No	No	No
ZNF804A	rs1344706	Yes (both)	No	AP efficacy	AP response
ZNF804A	rs12476147	No	No	No	No
ZNF804A	rs4667001	No	No	No	No
ZNF804A	rs1366842	No	No	No	No
ZNF804A	rs12477430	No	No	No	No

Yes = Previously associated with brain structure and/or antipsychotic response; No = Not reported in database, or not previously associated with brain structure or antipsychotic response in literature; AP = Antipsychotic; Both = Previously associated with both brain structure and antipsychotic response in literature; ADRs = Adverse drug reactions; AP prolactin = Antipsychotic-induced hyperprolactinemia.

Results coloured in blue fulfilled the defined criteria for prioritisation.

Table S6. Summary of predicted regulatory impact of all prioritised variants.

Gene	SNP rsID	Regul-omeDB	Poly-miRTS	SNP-2TFBS	rSNPBase				
					rSNP	Proximal	Distal	RNA BP mediated	eQTL
BDNF	rs6265	6	*ND*	No	Yes	Yes	No	Yes	Yes
BDNF	rs11030104	*ND*	*ND*	No	Yes	Yes	No	Yes	Yes
BDNF	rs10835210	3a	*ND*	No	Yes	No	No	Yes	No
BDNF	rs988748	4	*ND*	Yes	Yes	Yes	Yes	Yes	No
CACNA1C	rs11062040	3a	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs2429127	*ND*	*ND*	Yes	Yes	Yes	Yes	No	No
CACNA1C	rs10161032	5	*ND*	Yes	Yes	Yes	Yes	No	No
CACNA1C	rs765125	5	*ND*	Yes	Yes	Yes	Yes	No	No
CACNA1C	rs11062093	2b	*ND*	No	Yes	No	Yes	Yes	Yes
CACNA1C	rs7297992	5	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs6489348	4	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs4126711	4	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs2238034	5	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs10848635	5	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs1016388	2c	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs11062162	5	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs2007044	4	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs1006737	5	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs10848645	2b	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs10774037	2b	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs3819536	5	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs2238070	5	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs2239056	4	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs740417	*ND*	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs10491964	3a	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs2370515	5	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs4765687	2b	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs4765937	1f	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs2239084	*ND*	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs1015287	3a	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs10848665	*ND*	*ND*	Yes	Yes	Yes	No	Yes	No
CACNA1C	rs2238087	*ND*	*ND*	No	Yes	No	No	Yes	No
CACNA1C	rs11062260	5	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs4394887	5	*ND*	Yes	Yes	No	No	Yes	No
CACNA1C	rs2239118	5	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs1034936	5	*ND*	No	Yes	No	No	Yes	Yes
CACNA1C	rs4765961	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs2370602	5	*ND*	Yes	Yes	No	No	Yes	Yes
CACNA1C	rs215976	5	*ND*	No	Yes	No	No	Yes	No
CACNA1C	rs2238096	2b	*ND*	Yes	Yes	Yes	No	Yes	Yes
CACNA1C	rs2302729	2b	*ND*	No	Yes	Yes	Yes	Yes	Yes
CACNA1C	rs10848683	5	*ND*	No	No	No	No	No	Yes
CACNA1C	rs4765970	2b	*ND*	Yes	Yes	No	No	Yes	No
COMT	rs9606186	3a	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs2075507	5	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs2020917	4	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs737866	2b	*ND*	Yes	Yes	Yes	Yes	Yes	Yes
COMT	rs737865	2b	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs933271	4	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs174674	1f	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs5993883	*ND*	*ND*	No	Yes	Yes	No	Yes	Yes
COMT	rs740603	3a	*ND*	No	Yes	Yes	Yes	Yes	No
COMT	rs165656	4	*ND*	Yes	Yes	Yes	Yes	Yes	No
COMT	rs165722	3a	*ND*	No	Yes	Yes	Yes	Yes	No
COMT	rs6269	1a	*ND*	Yes	Yes	Yes	Yes	Yes	No
COMT	rs4633	2b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
COMT	rs2239393	1b	*ND*	Yes	Yes	Yes	Yes	Yes	Yes
COMT	rs4818	4	*ND*	No	Yes	Yes	Yes	Yes	No
COMT	rs4680	4	*ND*	No	Yes	Yes	Yes	Yes	Yes
COMT	rs174697	2b	*ND*	Yes	Yes	No	Yes	Yes	No
COMT	rs165599	4	Yes	No	Yes	Yes	Yes	Yes	No
COMT	rs165728	4	Yes	No	Yes	Yes	Yes	Yes	Yes
COMT	rs9265	2b	*ND*	No	Yes	Yes	Yes	Yes	No
DISC1	rs1417584	*ND*	*ND*	Yes	Yes	Yes	No	Yes	Yes

DISC1	rs2487453	5	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs4658883	3a	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs12066910	6	*ND*	Yes	Yes	No	No	Yes	No
DISC1	rs10864695	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs2492367	5	*ND*	No	Yes	Yes	No	Yes	Yes
DISC1	rs2812391	2b	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs16854954	5	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs17766087	2b	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs9803690	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs1322784	2b	*ND*	No	Yes	No	No	Yes	No
DISC1	rs2255340	2b	*ND*	No	Yes	No	No	Yes	No
DISC1	rs2738875	5	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs6675281	4	*ND*	No	Yes	Yes	No	Yes	No
DISC1	rs1535530	4	*ND*	No	Yes	Yes	No	Yes	Yes
DISC1	rs1000730	2b	*ND*	No	Yes	No	No	Yes	No
DISC1	rs7552697	4	*ND*	Yes	Yes	No	No	Yes	No
DISC1	rs12757857	6	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs3082	4	Yes	No	Yes	Yes	No	Yes	Yes
DISC1	rs1407601	3a	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs2356606	5	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs4658889	6	*ND*	Yes	Yes	No	Yes	Yes	No
DISC1	rs9431714	4	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs821722	4	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs7541019	6	*ND*	Yes	Yes	No	No	Yes	No
DISC1	rs11584798	3a	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs701158	2b	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs701160	1f	*ND*	No	Yes	No	No	Yes	Yes
DISC1	rs821615	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs821616	5	*ND*	No	Yes	Yes	No	Yes	No
DISC1	rs821631	5	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs821639	5	*ND*	No	Yes	No	No	Yes	No
DISC1	rs9729194	6	*ND*	Yes	Yes	No	No	Yes	Yes
DISC1	rs11122396	3a	*ND*	No	Yes	Yes	No	Yes	No
DISC1	rs16856322	*ND*	*ND*	No	Yes	Yes	No	Yes	Yes
DRD2	rs1800497	4	*ND*	No	Yes	No	No	Yes	No
DRD2	rs6278	5	Yes	No	Yes	Yes	No	Yes	No
DRD2	rs6277	5	*ND*	No	Yes	No	No	Yes	No
DRD2	rs6275	5	*ND*	No	Yes	No	No	Yes	Yes
DRD2	rs1076560	5	*ND*	Yes	Yes	No	No	Yes	No
DRD2	rs12363125	1c	*ND*	No	Yes	No	No	Yes	Yes
DRD2	rs1800498	5	*ND*	No	Yes	Yes	No	Yes	No
DRD2	rs1079597	5	*ND*	No	Yes	Yes	No	Yes	No
DRD2	rs2471857	1f	*ND*	No	Yes	Yes	Yes	Yes	Yes
DRD2	rs4436578	5	*ND*	Yes	Yes	No	No	Yes	Yes
DRD2	rs4245146	2b	*ND*	No	Yes	No	No	Yes	No
DRD2	rs7131056	*ND*	*ND*	No	Yes	No	No	Yes	Yes
DRD2	rs4630328	5	*ND*	Yes	Yes	No	No	Yes	No
DRD2	rs1799978	5	*ND*	No	Yes	Yes	No	No	No
DRD2	rs2514218	6	*ND*	Yes	No	No	No	No	Yes
DRD3	rs167771	5	*ND*	No	Yes	No	No	Yes	No
DRD3	rs6280	5	*ND*	No	Yes	No	No	Yes	No
DRD3	rs9825563	6	*ND*	Yes	Yes	Yes	No	No	Yes
DRD3	rs1394016	6	*ND*	Yes	No	No	No	No	Yes
DTNBP1	rs1047631	1d	Yes	No	Yes	Yes	No	No	Yes
DTNBP1	rs4712253	2b	*ND*	No	No	No	No	No	Yes
DTNBP1	rs2619522	6	*ND*	Yes	Yes	No	Yes	No	No
DTNBP1	rs2619536	*ND*	*ND*	Yes	Yes	Yes	Yes	No	No
IL1RN	rs315920	*ND*	*ND*	Yes	Yes	Yes	No	No	Yes
IL1RN	rs423904	3a	*ND*	Yes	No	No	No	No	No
IL1RN	rs3087266	2c	*ND*	Yes	No	No	No	No	Yes
IL1RN	rs315952	*ND*	*ND*	No	No	No	No	No	Yes
NRG1	rs35753505	6	*ND*	Yes	No	No	No	No	No
NRG1	rs6994992	5	*ND*	No	Yes	Yes	No	No	No
NRG1	rs28401439	5	*ND*	Yes	Yes	Yes	No	No	No
NRG1	rs6987996	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs4733094	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs16878394	5	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs796549	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs7002063	5	*ND*	Yes	Yes	No	No	Yes	Yes

NRG1	rs2010243	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs1462900	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs1381874	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs7841220	6	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs10503899	*ND*	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs11776959	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs10503901	2b	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs1481728	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs4733313	5	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs900102	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs16879067	5	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs17624592	2b	*ND*	No	Yes	No	No	Yes	No
NRG1	rs11778887	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs7005124	3a	*ND*	No	Yes	No	No	Yes	No
NRG1	rs1685117	5	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs7841599	5	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs970998	2b	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs1565031	4	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs1623372	1d	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs16879304	2b	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs939077	5	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs4733325	*ND*	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs3847131	6	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs9297192	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs17716295	6	*ND*	No	Yes	No	No	Yes	No
NRG1	rs12216802	1f	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs17645417	3b	*ND*	No	Yes	No	No	Yes	No
NRG1	rs7844425	1f	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs4733347	5	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs4733130	2b	*ND*	No	Yes	No	No	Yes	No
NRG1	rs2439312	1f	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs17721043	1f	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs2439292	1f	*ND*	No	Yes	No	No	Yes	Yes
NRG1	rs3924999	*ND*	*ND*	Yes	Yes	No	No	Yes	No
NRG1	rs2919370	5	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs2466049	5	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs2919392	2c	*ND*	No	Yes	No	No	Yes	No
NRG1	rs2919390	6	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs2976532	*ND*	*ND*	Yes	Yes	No	No	Yes	Yes
NRG1	rs73672607	6	*ND*	No	Yes	Yes	No	Yes	No
OXTR	rs237884	*ND*	Yes	No	Yes	Yes	No	Yes	No
OXTR	rs237885	6	*ND*	Yes	Yes	No	No	Yes	No
OXTR	rs11706648	5	*ND*	No	Yes	No	No	Yes	No
OXTR	rs237888	3a	*ND*	No	Yes	No	No	Yes	Yes
OXTR	rs4686301	5	*ND*	No	Yes	No	No	Yes	No
OXTR	rs237889	1f	*ND*	No	Yes	No	Yes	Yes	No
OXTR	rs2268495	2b	*ND*	No	Yes	No	No	Yes	Yes
OXTR	rs237899	5	*ND*	No	Yes	Yes	No	Yes	No
OXTR	rs4686302	4	*ND*	No	Yes	Yes	Yes	Yes	Yes
RGS4	rs951439	3a	*ND*	No	Yes	Yes	No	No	No
RGS4	rs2661319	4	*ND*	No	Yes	Yes	No	Yes	Yes
RGS4	rs10759	5	*ND*	No	Yes	Yes	No	Yes	Yes
TNF-α	rs1800629	1d	*ND*	Yes	No	No	No	No	Yes
TNF-α	rs1800630	2b	*ND*	No	No	No	No	No	Yes
ZNF804A	rs1344706	*ND*	*ND*	No	Yes	No	No	Yes	Yes
ZNF804A	rs12476147	*ND*	*ND*	No	Yes	No	No	Yes	Yes
ZNF804A	rs4667001	5	*ND*	No	Yes	No	No	Yes	No
ZNF804A	rs1366842	5	*ND*	No	Yes	No	No	Yes	Yes
ZNF804A	rs12477430	5	*ND*	Yes	Yes	No	No	Yes	No

ND = Not determined; rSNP = Regulatory single nucleotide polymorphism; Proximal = Proximal regulation; Distal = Distal regulation; RNA BP mediated = RNA binding protein mediated regulation; eQTL = Expression quantitative trait loci; Yes = Involved in regulatory category; No = Not involved in regulatory category.
Results coloured in blue fulfilled the defined criteria for prioritisation.

Tables S7a – e. Linkage disequilibrium (LD) plots for genes where two or more variants in LD with one another (as defined by D' > 0.8) were significantly associated with antipsychotic treatment response.

Table S7a. LD plot showing D' values between all variants in *NRG1* that were significantly associated with antipsychotic treatment response in this study.

	rs6987996	rs4733094	rs796549	rs10503901	rs1481728	rs16879067	rs11778887	rs7005124	rs16879304	rs3847131	rs17645417	rs2439312	rs3924999	rs2466049	rs2919392
rs6987996	.	0.8282	0.1003	0.0017	0.0424	0.1195	0.0950	0.1885	0.4429	0.0687	0.0934	0.0459	0.1295	0.4763	0.1498
rs4733094	.	.	0.9984	0.3509	0.3627	0.2188	0.3809	0.1511	0.9973	0.4014	0.1637	0.1251	0.2112	0.9959	0.4078
rs796549	.	.	.	0.3133	0.0719	0.9983	0.6249	0.3717	0.3416	0.2102	0.0066	0.4090	0.5633	0.1409	0.0726
rs10503901	.	.	.	.	0.2437	0.3195	0.4338	0.6799	0.0020	0.1459	0.0113	0.7161	0.6848	0.4870	0.1658
rs1481728	.	.	.	.	.	0.7039	0.7249	0.6584	0.0486	0.0893	0.1610	0.1911	0.5000	0.1079	0.1879
rs16879067	.	.	.	.	.	.	0.8076	0.6213	0.9981	0.2803	0.0851	0.0281	0.1630	0.2183	0.2125
rs11778887	.	.	.	.	.	.	.	0.4603	0.9977	0.3160	0.2282	0.1779	0.2468	0.7679	0.3177
rs7005124	.	.	.	.	.	.	.	.	0.9983	0.0101	0.1585	0.2566	0.1180	0.1792	0.1910
rs16879304	.	.	.	.	.	.	.	.	.	0.4975	0.0744	0.6742	0.8956	0.0826	0.0049
rs3847131	.	.	.	.	.	.	.	.	.	.	0.3790	0.3348	0.4310	0.1745	0.0080
rs17645417	.	.	.	.	.	.	.	.	.	.	.	0.8415	0.2137	0.4660	0.0191
rs2439312	.	.	.	.	.	.	.	.	.	.	.	.	0.2621	0.6841	0.0704
rs3924999	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9979	0.1465
rs2466049	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.7987
rs2919392	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

D' values > 0.8 are highlighted in red, indicating that the corresponding variants are in pairwise LD.

Table S7b. LD plot showing D' values between all variants in *COMT* that were prioritised for investigation in this study.

	rs9606186	**rs2075507**	**rs2020917**	**rs737866**	**rs737865**	**rs933271**	rs174674	rs5993883	rs740603	rs165656	rs165722	rs6269	rs4633	**rs2239393**	**rs4818**	rs4680	rs174697	rs165599	rs165728	rs9265
rs9606186	.	0.9755	0.9991	0.9991	0.9991	0.8433	0.8313	0.8591	0.5868	0.3451	0.4180	0.2383	0.3430	0.3528	0.4250	0.3809	0.6386	0.2806	0.7194	0.3072
rs2075507	.	.	0.9991	0.9991	0.9991	0.9444	0.9399	0.9245	0.6626	0.3130	0.3881	0.2440	0.3486	0.4071	0.3357	0.3787	0.5500	0.2517	0.6532	0.3049
rs2020917	.	.	.	0.964	0.964	0.9993	0.9993	0.7909	0.6188	0.5710	0.4949	0.4823	0.5125	0.6747	0.6361	0.7820	0.4918	0.0750	0.0222	0.0523
rs737866	.	.	.	.	0.9996	0.9347	0.9212	0.8143	0.5369	0.6999	0.4936	0.4856	0.5739	0.7008	0.6759	0.8044	0.2126	0.0660	0.0043	0.0438
rs737865	.	.	.	.	.	0.9347	0.9212	0.8143	0.5369	0.6999	0.4936	0.4856	0.5739	0.7008	0.6759	0.8044	0.2126	0.0660	0.0043	0.0438
rs933271	.	.	.	.	.	.	0.9855	0.4608	0.0229	0.0503	0.0225	0.4574	0.0155	0.5188	0.8768	0.0216	0.4358	0.3509	0.1553	0.3090
rs174674	.	.	.	.	.	.	.	0.5449	0.0700	0.0173	0.0125	0.4446	0.0689	0.4809	0.8487	0.0553	0.2886	0.3305	0.1249	0.2848
rs5993883	.	.	.	.	.	.	.	.	0.5908	0.0403	0.0933	0.2598	0.1187	0.2504	0.1341	0.1463	0.6987	0.2423	0.2710	0.2098
rs740603	.	.	.	.	.	.	.	.	.	0.3475	0.3170	0.3039	0.3370	0.3829	0.4976	0.3625	0.6425	0.1812	0.2317	0.2029
rs165656	.	.	.	.	.	.	.	.	.	.	0.8044	0.5460	0.9513	0.6060	0.9994	0.9997	0.8617	0.3203	0.8848	0.3495
rs165722	.	.	.	.	.	.	.	.	.	.	.	0.9997	0.9481	0.8145	0.7976	0.9997	0.7200	0.3213	0.6711	0.3514
rs6269	.	.	.	.	.	.	.	.	.	.	.	.	0.9996	0.9998	0.6807	0.9996	0.9987	0.1327	0.2887	0.1706
rs4633	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9996	0.8621	0.9997	0.8277	0.3551	0.9988	0.3848
rs2239393	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9063	0.9995	0.6375	0.1157	0.2164	0.1464
rs4818	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9992	0.4284	0.1594	0.0001	0.1061
rs4680	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.7859	0.3608	0.9987	0.4158
rs174697	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9989	0.5269	0.9990
rs165599	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9988	0.9997
rs165728	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.9989
rs9265	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Variants in bold typeset were significantly associated with antipsychotic treatment response in this study.
D' values > 0.8 are highlighted in red, indicating that the corresponding variants are in pairwise LD.

Table S7c. LD plot showing D' values between all variants in *DRD3* that were prioritised for investigation in this study.

	rs167771	**rs6280**	**rs9825563**	**rs1394016**
rs167771	.	0.708	0.4888	0.9697
rs6280	.	.	0.9069	0.9998
rs9825563	.	.	.	0.9997
rs1394016	.	.	.	.

Variants in bold typeset were significantly associated with antipsychotic treatment response in this study.
D' values > 0.8 are highlighted in red, indicating that the corresponding variants are in pairwise LD.

Table S7d. LD plot showing D' values between all variants in *OXTR* that were prioritised for investigation in this study.

	rs237884	**rs237885**	**rs11706648**	**rs237888**	**rs4686301**	rs237889	rs2268495	rs237899	rs4686302
rs237884	.	0.1777	0.7275	0.8425	0.6912	0.6636	0.0471	0.3027	0.2941
rs237885	.	.	0.9994	0.5329	0.9196	0.8174	0.0906	0.1388	0.0239
rs11706648	.	.	.	0.8231	0.9664	0.9990	0.0693	0.1068	0.3374
rs237888	.	.	.	.	0.9991	0.8332	0.1065	0.7739	0.3359
rs4686301	.	.	.	.	.	0.9980	0.0330	0.1172	0.2344
rs237889	.	.	.	.	.	.	0.0658	0.2513	0.0741
rs2268495	.	.	.	.	.	.	.	0.9993	0.9383
rs237899	.	.	.	.	.	.	.	.	0.9984
rs4686302	.	.	.	.	.	.	.	.	.

Variants in bold typeset were significantly associated with antipsychotic treatment response in this study.
D' values > 0.8 are highlighted in red, indicating that the corresponding variants are in pairwise LD.

Table S7e. LD plot showing D' values between all variants in *DISC1* that were significantly associated with antipsychotic treatment response in this study.

	rs2487453	rs7552697	rs12757857	rs1407601	rs701160
rs2487453	.	0.433	0.4241	0.1173	0.1889
rs7552697	.	.	0.9994	0.2695	0.2365
rs12757857	.	.	.	0.9988	0.1986
rs1407601	.	.	.	.	0.3036
rs701160	.	.	.	.	.

D' values > 0.8 are highlighted in red, indicating that the corresponding variants are in pairwise LD.

APPENDIX B

Conference outputs

Poster presentation

Frickel, E., O'Connell, K.S., du Plessis, S., Rhode, C., Emsley, R.A., Warnich, L., McGregor, N.W. 2018. Structural imaging genetics of antipsychotic treatment response in schizophrenia. Stellenbosch University Faculty of Medicine and Health Sciences' Annual Academic Day. 29 August. Tygerberg, South Africa.

Oral presentations

Frickel, E., O'Connell, K.S., du Plessis, S., Rhode, C., Emsley, R.A., Warnich, L., McGregor, N.W. 2018. Investigating the interplay between genetic and neuroanatomical variation in antipsychotic treatment response. The First Conference of Biomedical and Natural Sciences and Therapeutics (CoBNeST). 7-10 October. Stellenbosch, South Africa.

Frickel, E., O'Connell, K.S., du Plessis, S., Rhode, C., Emsley, R.A., Warnich, L., McGregor, N.W. 2019. The effects of gene-environment interactions with childhood trauma on brain structure and antipsychotic treatment response. The 18th Biennial Congress of the Southern African Society for Human Genetics (SASHG). 3-6 August. Cape Town, South Africa.