Antisocial Behaviour and Depressed Mood: Associations from Adolescence to Adulthood

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Abstract

Antisocial behaviour and depression co-occur more often than would be expected by chance. Different mechanisms may account for the association including shared risk factors, shared genetic effects and causal developmental pathways from one trait to another. Identifying mechanisms involved in the association of antisocial behaviour and depression is imperative given that this might indicate approaches to treating these serious disorders. Many studies have addressed cross-sectional associations, with limited research on the longitudinal association. In this thesis, three studies were carried out to investigate the association between antisocial behaviour and depressed mood at three different time points (mean ages: 15, 17, and 20 years). The analyses are based on the G1219 longitudinal study of 3,640 adolescent twins and siblings. In the first study (Chapter 2), longitudinal associations were examined to investigate the directionality of the association between the two traits using cross-lagged autoregressive pathway models. Strong cross-sectional associations were found, in addition to significant cross-trait association from depressed mood to oppositionality. In the second study (Chapter 3), a multivariate genetically informative design (Cholesky decomposition) was used to investigate these strong cross-sectional associations. Overlapping genetic effects were found between antisocial behaviour and depressed mood. Considering the results of the second study, the third study (Chapter 4) investigated the role of functional variants of candidate genes (GNβ3, 5HTTLPR and COMT) in the association between both traits. Only GNβ3 was associated with depressed mood, however none of the candidate genes examined showed associations with both antisocial behaviour and depressed mood. Overall, the findings from the first two studies supported phenotypic and genetic overlaps. However, results of third study did not provide evidence on the overlap between the traits. Further replication with additional genetic variants in different age groups is pertinent to uncover the mechanisms involved in the association.

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List of Abbreviations

Δdf	Change in degrees of freedom
$\Delta\chi^2$	Change in chi-square
ΔLL	Change in Log-Likelihood
-2LL	Minus twice the Log-Likelihood
5HT	Serotonin
5HTT	Serotonin transporter
5HTTLPR	Serotonin transporter linked promoter region
χ^2	Chi-square goodness-of-fit statistic
a	Cronbach's alpha
A	Adenine (in molecular genetics)
A	Additive genetic influence
a^2	Additive genetic variance
ADHD	Attention Deficit Hyperactivity Disorder
ASR	Adult Self-Report
AIC	Akaike Information Criterion
AL	Adolescent limited
ASB	Antisocial behaviour
β	Standardised beta coefficient
BDNF	Brain Derived Neurotrophic Factor
bp	Base pair
C	Cytosine (in molecular genetics)
C	Shared (common) environmental influence
c^2	Shared environmental variance

CBCL	Child Behavior Checklist
CD	Conduct Disorder
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
CL	Childhood Limited
COMT	Catechol-O-methyl transferase gene
CRHR1	CRH type 1 receptor
CU	Callous-Unemotional
d	Effect size
D	Non-additive genetic (dominance) influence
DAT	Dopamine transporter
DEL	Delinquency
DEP	Depressed mood
df	Degrees of freedom
DNA	Deoxyribonucleic Acid
DRD1	Dopamine Receptor D1
DRD2	Dopamine Receptor D2
DRD3	Dopamine Receptor D3
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
DZ	Dizygotic twins
E	Non-shared environmental influence
e^2	Non-shared environmental variance
ExE	Environment-environment interaction
EFA	Exploratory Factor Analyses

G	Guanine (in molecular genetics)
G1219	Genesis 12-19 years
GCTA	Genome Wide Complex Trait Analysis
GNβ3	Guanine nucleotide binding protein beta 3
GWAS	Genome Wide Association Studies
GxE	Gene-environment interaction
HTR1A	Serotonin receptor 1A
HTR1B	Serotonin receptor 1B
HTR2A	Serotonin receptor 2A
HWE	Hardy-Weinberg Equilibrium
kb	Kilobase
LCP	Life-Course Persistent
L	Long allele
LL	Long-Long
LS	Long-Short
MAOA	Monoamine Oxidase-A
MDD	Major Depressive Disorder
Met	Methionine
MPNI	Multidimensional Peer Normative Inventory
MMPI-2	Minnesota Multiphasic Personality Inventory-2
MZ	Monozygotic twins
N	Number of participants
ODD	Oppositional Defiant disorder
OPP	Oppositionality
OR	Odds Ratio

p	Probability
PCR	Polymerase Chain Reaction
PRS	Polygenic Risk Score
r	Correlation coefficient
rMZ	Monozygotic twins' correlation
rDZ	Dizygotic twins' correlation
rGE	Gene-environment correlation
RMSEA	Root Mean Square Error of Approximation
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Model
SERT	Serotonin transporter
Sib	Siblings
SIBS	Sibling Interaction and Behavior Study
SLC6A4	Serotonin transporter gene (solute carrier family 6, member 4)
SMFQ	Short version of the Mood and Feeling Questionnaire
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for the Social Sciences
S	Short allele
SSRI	Selective Serotonin Reuptake Inhibitor
SS	Short-Short
t	t-statistic
T	Thymine (in molecular genetics)
T	Time point
TLI	Tucker-Lewis Index

Val	Valine
VNTR	Variable Number Tandem Repeat
WLSE	Weight Least Square Estimator
YSR	Youth Self Report

Chapter 1 Background

1.1 Overview

This chapter will provide an overview of the current literature on antisocial behaviour and depression from epidemiological and clinical studies. This consists of seven sections that covers research related to the thesis question and aims. The first section provides a general introduction to the association between antisocial behaviour and depression. Antisocial behaviour and depression will be reviewed separately in the second and third section of this chapter. The fourth section covers the comorbidity of antisocial behaviour and depression addressing sex differences and aetiological evidence. The fifth section covers existing models which attempt to explain the different paths involved in the association. Rational for this thesis based on the current literature and the sample information from G1219 dataset at each time point are discussed in the final two sections respectively.

1.2 Antisocial behaviour

Antisocial behaviour refers to behaviour which violates human rights and societal rules (Burt, Donnellan, Iacono, & McGue, 2011; Rutter, Giller, & Hagell, 1998). These include behaviours such as: setting fires, theft, crime, assault and other delinquent acts (Gaik, Abdullah, Elias, & Uli, 2010). Antisocial behaviour at a young age has a number of negative outcomes (e.g. cannabis use, general health problems) (Bor, McGee, Hayatbakhsh, Dean, & Najman, 2010). An increase in the number of children and adolescents with antisocial behaviour was reported internationally over 25 year period, assessed in 1974, 1986 and 1999 (Collishaw, Maughan, Goodman, & Pickles, 2004; Ford, 2004). This most commonly occurs during adolescence as compared to other life stages (Moffitt, 1993). However, antisocial behaviour was reported to be stabilised in the recent years (Chaplin, Flatley, & Smith, 2011). Nonetheless, it was estimated that antisocial behaviour has direct and indirect financial costs in children at £15,382 per family (inflation corrected for 2016 to approximately £24,457), with 37% of the burden taken by their family (Knapp, Scott, & Davies, 1999).

1.2.1 The heterogeneity of antisocial behaviour

Antisocial behaviour is heterogeneous consisting of various subtypes. According to the developmental taxonomic theory proposed by Moffitt (1993), there are two distinct groups of antisocial behaviour differing in aetiology, course, prognosis, classification and correlates: a Life-Course Persistent (LCP) group and an Adolescent-Limited (AL) group. The LCP group show stable levels of aggression beginning in childhood and remaining stable across their life span. Neuropsychological impairments and adverse family life are important risk factors responsible for antisocial behaviour in the LCP group (Moffitt, 2007). Neuropsychological deficits can result from a number of factors including genetic and postnatal influences (Beaver, DeLisi, Vaughn, & Wright, 2010; Cauffman, Steinberg, & Piquero, 2005; McGloin, Pratt, & Piquero, 2006; Raine, 2008). The adverse family environments interact with the neuropsychological impairments which increase the risk for an individual to fall into the LCP path (Turner, Hartman, & Bishop, 2007). The AL group is limited to the adolescent stage and is nonaggressive and does not involve neuropsychological impairment (Moffitt, 1993). The maturity gap has been discussed as a cause of AL offending, this refers to the frustration created by the distance between biological and social maturity (Agnew, 2003). With increasing age, social maturity aligns with biological maturity and hence, AL offending ceases which prevents continuation into adulthood (Hussong, Curran, Moffitt, Caspi, & Carrig, 2004). A large number of studies supported Moffitt's taxonomy on the two distinct subgroups within antisocial behaviour (Piquero, 2001; Raine et al., 2005). A third group is referred to as abstainers who display undesirable personality traits (e.g. withdrawn, overly constrained, overly shy), they avoid the maturity gap and desist from delinquent peer contact (Moffitt, 1993). Genetic factors was found to play a role in LCP, AL and abstainers groups (Barnes, Beaver, & Boutwell, 2011). Greater influence of genetic factors was reported for the LCP offender groups and abstainer offender group compared to the AL offender group. Childhood Limited (CL) was also included as an additional subgroup to account for individuals who show high level of engagement in antisocial behaviour in childhood which declines in adolescence (Aguilar, Sroufe, Egeland, & Carlson, 2000; Fergusson, Horwood, & Nagin, 2000; Odgers et al., 2008; Raine et al., 2005). In line with this theory, Dunedin Cohort Study found that individuals in the CL group experienced similar problems during childhood to individuals in the LCP group but to a lesser extent, and demonstrated declining levels of antisocial behaviour in adolescence (Moffitt, 2006).

In the current fifth edition of the Diagnostic and Statistical Manual (DSM-5), antisocial behaivour has been categorised into Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD). CD is focussed on severe forms of antisocial behaviour involving aggression towards people or animals, destruction of property, theft and deceit. On the other hand, ODD involves problems of emotional dysregulation, i.e. angry/irritable mood (American Psychaitric Association., 2013). Long term negative outcomes has been reported for CD and ODD in a longitudinal study of 177 clinically referred boys aged 7-12 years who were annually followed to age 24 (Burke, Rowe, & Boylan, 2014). ODD symptoms from childhood to adolescence predicted poorer functioning with peers, romantic relationships, paternal and maternal relationships in adulthood. Symptoms of CD predicted workplace problems, poor maternal relationship, lower academic attainment and violent injuries (Burke et al., 2014). ODD forms at an early stage of CD development and is considered as a milder form of CD. As ODD is a precursor to CD and a risk factor for later CD, it would be expected to be present earlier in development (Loeber, Green, Lahey, Christ, & Frick, 1992; Rowe, Maughan, Pickles, Costello, & Angold, 2002).

Other approaches to sub-typing CD include distinguishing those with and without high levels of callous-unemotional (CU) traits. CU traits involve lack of empathy, guilt and callous use of others for one's own gain (Barry, Barry, Deming, & Lochman, 2008; Essau, Sasagawa, & Frick, 2006; Frick & White, 2008; Viding, Jones, Frick, Moffitt, & Plomin, 2008). The DSM-5 includes CU traits as a clinical specifier to describe a subgroup of youth with CD, which is designed to identify those with severe and persistent difficulties (Frick & Moffitt, 2010). Genetic overlap has been found between CU and conduct problems in boys and girls which explain the phenotypic relationship (Viding, Frick, & Plomin, 2007). A more severe form of antisocial behaviour is associated with CU traits (Frick, Ray, Thornton, & Kahn, 2014). More specifically, early onset antisocial behaviour has been associated with CU traits (Dandreaux & Frick, 2009; Silverthorn, Frick, & Reynolds, 2001).

Another approach to parsing the heterogeneity in CD is to subdivide them into aggressive (physical harm to others) and non-aggressive delinquent behaviour (damage to property, deceit or violation of norms) (Burt et al., 2011; Matthys & Lochman, 2010; Tackett, Krueger, Iacono, & McGue, 2005). It has been argued that the distinction of aggressive and non-aggressive antisocial behaviour especially during childhood provides an accurate account of antisocial behaviour instead of a unitary CD construct (Tackett, Krueger, Sawyer, & Graetz, 2003). There are also different developmental trajectories between aggressive and non-aggressive behaviour subtypes (Stanger, Achenbach, & Verhulst, 1997). For example, Stanger et al. (1997), in a longitudinal study, found that aggressive and nonaggressive delinquent behaviours were similar in their rate from age 4 to 10 years. However, beyond this age, aggressive behaviour was reported to decline whilst non-aggressive delinquent behaviours increased up to age 17 years.

Within ODD heterogeneity was reported by Stringaris and Goodman (2009a) showing that there are three dimensions: hurtfulness, being headstrong and irritability. These dimensions show differential associations with other forms of psychopathology. For example, irritable-ODD has been associated with depression (Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009b); hurtful-ODD associated with aggression (Stringaris & Goodman, 2009a); and headstrong-ODD associated with CD (Rowe et al., 2010; Stringaris & Goodman, 2009a, 2009b). A two-dimensional ODD model was proposed following this including the irritable and hurtful dimensions (Burke & Loeber, 2010; Rowe et al., 2010; Stringaris et al., 2012).

1.2.2 Measuring antisocial behaviour

Several techniques have been employed to measure antisocial behaviour including observations in adolescents natural setting (e.g. school, home, peer groups), in clinic or laboratories (Moffitt, 2005). This assessment technique provides an advantage for obtaining useful information about an adolescent's behaviour which is not filtered through the perceptions of an informant. However, these also pose a problem of being time-consuming and carry a high cost to run and difficulty of reliably identifying covet behaviour (e.g. theft) through observation (Thomas & Pope, 2013).

Another method for assessing antisocial behaviour is diagnostic interviews which includes semi-structured and structured forms. Diagnostic interviews provide a reliable means of assessing emotional and behavioural functioning. However, diagnostic interviews are often time-intensive, and they do not provide any norm-referenced information. These forms of interviews also do not include a format for obtaining information from a child's teacher and their reliability is questionable (Thomas & Pope, 2013).

Behaviour rating scales are also used to assess antisocial behaviour, there are a number of standardised instruments such as the Child Behaviour Checklist (CBCL) (Achenbach, 1991), Youth Self-Report (YSR) (Achenbach, 1991), Adult Self-Report (ASR) (Achenbach & Rescorla, 2003), Multidimensional Peer Nomination Inventory (MPNI) (Pulkkinen, Kaprio, & Rose, 1999) and Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1999). These assessments are considered useful in screening a broad range of antisocial behaviours (Bendixen, Endresen, & Olweus, 2003; Reitman, Hummel, Franz, & Gross, 1998). These measures can be used in multiple forms including self-reports, parent reports, peer reports, and teacher reports. In order to obtain a comprehensive view of an adolescents' behaviour, multiple informants are required from different perspectives and in different reference groups. However, adolescents are the most important informants as their parents are not always aware of their covert behaviour (Lahey et al., 2000; Romano, Tremblay, Vitaro, Zoccolillo, & Pagani, 2001; Rutter et al., 1998). The instrument relevant to the current thesis will be the self-report measures including: the YSR (for ages 11-18) completed by adolescents (Achenbach, 1991), and ASR (for ages 18-59) completed by young adults (Achenbach & Rescorla, 2003).

1.2.3 Sex difference in antisocial behaviour

A number of studies have documented sex differences in antisocial behaviour (Bennett, Farrington, & Huesmann, 2005; Berkout, Young, & Gross, 2011; Lahey et al., 2006; Moffitt, 1993; Tremblay, 2010). Greater levels of antisocial behaviour have been reported for males than females, with a higher number of males engaging in extreme forms of antisocial behaviour as compared to females (Berkout et al., 2011; Bor et al., 2010; Moffitt & Caspi, 2001). Differences in boys and girls are also evident developmentally in terms of age. Specifically, antisocial behaviour typically emerges earlier for boys (9-12 years) than girls (14-15 years) (Silverthorn & Frick, 1999; Silverthorn et al., 2001). However, no genetic and shared environmental sex-specific effects have been found in the development of antisocial behaviour among boys and girls (Rhee & Waldman, 2002).

1.2.4 Aetiology of antisocial behaviour

1.2.4.1 Genetic

Studies with different assessment methods, age of assessment and different approaches have reported strikingly similar genetic and environmental influences on the emergence of antisocial behaviour (Lahey & Waldman, 2012; Rhee & Waldman, 2002, 2010). Meta-analyses have shown that heritability estimates for antisocial behaviour range between .41 - .56 (Ferguson, 2010; Rhee & Waldman, 2002). Rhee and Waldman (2002) conducted a meta-analysis of 51 twins and adoption studies finding an overall 41% genetic influence on antisocial behaviour. In a later meta-analysis of twin studies, genetic factors were found to account for 56% of the variance in antisocial behaviour, unique environmental influence accounted for 31% and shared environment accounted for 11% (Ferguson, 2010). These reviews demonstrate that genetic influences can explain approximately half of the variance in antisocial behaviour with the remaining variance explained by environmental influences.

Different heritability estimates have been reported for different forms of antisocial behaviour (aggressive vs. nonaggressive behaviour). Genetic and nonshared environmental factors reported to influence both types of antisocial behaviour, with one study showing that covariation between these behaviours could be explained by 61% genetic factors and 39% by nonshared environmental factors (Gelhorn et al., 2006). However, the effects of genetic and environmental factors differ developmentally for these forms of behaviour. For example, in a review of 103 twin and adoption studies, genetic influence was reported to be larger for aggressive behaviour (65%), with lower shared environmental (5%) and nonshared environmental factors (30%). Nonaggressive behaviours were also heritable (48%), but showed higher nonshared environment (34%) and shared environmental factor (18%) compared to aggressive form (Burt, 2009a). It was also reported that from childhood to adolescence the role of genetic factors for aggressive behaviour increased whereas nonshared environmental factors decreased. In one study, heritability for aggressive and non-aggressive antisocial behaviour *increased* between 9-18 years of age in males. On the other hand, heritability estimates for non-aggressive antisocial behaviour were found to *decrease* with increasing age in females (Wang, Niv, Tuvblad, Raine, & Baker, 2013).

The persistence of antisocial behaviour across time has been linked to a common set of genetic factors across childhood to adulthood (Tuvblad, Narusyte, Grann, Sarnecki, & Lichtenstein, 2011). The importance of genetic influence was found across a number of longitudinal studies from childhood to adolescence, showing a common genetic factor explaining the variance in antisocial behaviour (Jacobson, Prescott, & Kendler, 2002; Silberg, Rutter, Tracy, Maes, & Eaves, 2007; Van Hulle et al., 2009; Wichers et al., 2013).

There are a number of limitations in regards to the use of twin data. One of the main limitations concerns the generalisability of the twin designs (Plomin, DeFries, Knopik, & Neiderbiser, 2013). It is possible that twins differ from singletons in their levels of antisocial behaviour. However, comparisons between twins and singleton show no major difference in behaviour problems (Johnson, Krueger, Bouchard, & McGue, 2002; Kendler, Martin, Heath, & Eaves, 1995; Moilanen et al., 1999; Van Den Oord, Koot, Boomsma, Verhulst, & Orlebeke, 1995). Another limitation of the twin method concerns the equal environment assumption wherein it is assumed that the degree of environmental similarity is approximately the same for both types of twins. If this assumption is not met, there would be an artificial inflation of the heritability estimate. Family and adoption studies can be used to overcome these problems. However, family studies are unable to disentangle the relative weights of genetic and environmental factors. Adoption studies also carry limitations, these studies are problematic and scarce (Bouchard & McGue, 2003; Rueter, Keyes, Iacono, & McGue, 2009).

Furthermore, twin research identifies genetic variance in antisocial behaviour but the classic twin study design cannot identify the specific genes involved. Molecular genetics can help to identify the candidate genes implicated in the heritability of antisocial behaviour. Genes are a short section of the deoxyribonucleic acid (DNA) (Morizot & Kazemian, 2015). Variation in genes are referred to as polymorphisms with different versions referred to as alleles (Morizot & Kazemian, 2015). The way nerve impulses are transmitted and received by the brain are influenced by genes which operate via multiple pathways. This includes the serotonergic pathways (involved in brain development, appetite, mood and motor function), dopaminergic pathways (involved in reward system), and noradrenergic pathways (involved in the central arousal system) (Bartels, van de Aa, van Beijsterveldt, Middeldorp, & Boomsma, 2011; Morley & Hall, 2003; Reif & Lesch, 2003).

Antisocial behaviour is influenced by a number of genes involved in the serotonergic pathways (Morizot & Kazemian, 2015). Serotonin neurotransmitter (5HT[5-hydroxytryptamine]) is distributed in the brain and is involved in mood, appetite, cognition, emotion and motor functions (Cools, Roberts, & Robbins, 2008). Serotonergic neurons are located along the midline of the brain stem in the raphe nuclei which sends axons to all parts of the central nervous system (Lucki, 1998). SLC6A4 is composed of 14 exons spanning ~31 kilobases (kb) located on chromosome 17q11.2 (Lesch et al., 1996). The serotonin transporter linked region (5HTTLPR) is a polymorphic region in SLC6A4 gene, which consists of a 44 base pair (bp) insertion / deletion and is located on the 5-flanking arm ~1kb upstream of the 5HTT gene transcription initiation site (Lesch et al., 1996). This polymorphism has been associated with antisocial behaviour (Krakowski, 2003). The serotonin transporter is responsible for the reuptake of released serotonin from the synaptic cleft into nerve terminals (Gainetdinov & Caron, 2003). There are different allelic forms of this polymorphism, a short (S; 14 copies) and a long (L; 16 copies) variant, individuals can either be homozygous (SS / LL) or heterozygous (SL). The basal level of transcriptional efficacy of the 5HTT gene is much higher for the L allelic variant leading to increased serotonin uptake activity, which in turn leads to reduced availability of serotonin at the synapse. On the other hand, the S allelic variant of the polymorphism is associated with reduced transcriptional efficacy which leads to reduced uptake activity of serotonin and increased serotonin availability in the synapse (Kraft, Slager, McGrath, & Hamilton, 2005; Lesch et al., 1996).

The S allele of 5HTTLPR has been associated with violent offending and aggression in adolescents and adults (Douglas et al., 2011; Gerra et al., 2004; Hallikainen et al., 1999; Liao, Hong, Shih, & Tsai, 2004; Retz, Retz-Junginger, Supprian, Thome, & Rosler, 2004). A meta-analysis has also found an association between antisocial behaviour and the S allele of the 5HTTLPR (Ficks & Waldman, 2014). The effect size for the genetic variation did not differ by the specific antisocial behaviour phenotype which indicates that general antisocial behaviour is affected in the same way as specific traits such as aggression. In addition, results from this meta-analysis did not differ between community-based or clinically referred samples. The prevalence of the S allele differs among different ethnic backgrounds; the S allele is less prevalent among individuals of African ancestry (~.2) (Lotrich, Pollock, &

Ferrell, 2003) followed by Europeans (.4) (Gerra et al., 2005; Gonda et al., 2009), and highest among Asian ancestry (~.7) (Liao et al., 2004). The role of 5HTTLPR in relation to antisocial behaviour will be discussed in greater detail in Chapter 4.

Genetic variations in the dopaminergic pathways include the DAT1 gene (SLC63A) which encodes the dopamine transporter (DAT) variant number of tandem repeats (VNTR) polymorphism identified in the 15^{th} exon (Thomas & Pope, 2013). DAT1 VNTR has been associated with increased risk of antisocial characteristics (Guo, Roettger, & Shih, 2007). Other dopaminergic genes associated with antisocial behaviour include DRD3, DRD4, and DRD5. For example, DRD5 has been associated with ODD (Bachner-Melman et al., 2005), and the DRD2 gene has been associated with increase in delinquent involvement (Beaver et al., 2007).

Other genes involved in the production of enzymes for the metabolism of dopamine, epinephrine and norepinephrine are associated with antisocial behaviour include the catechol-O-methyl transferase gene (COMT) (Morizot & Kazemian, 2015). COMT is involved in the production of dopamine (Thomas & Pope, 2013). The COMT gene consists of a SNP at codon 158 in the fourth exon of the membrane-bound form of COMT. The COMT contains a guanine (G) to adenine (A) mutation that results in substitution of methionine (Met) for valine (Val) in enzyme synthesis. The Val allele has been associated with CD (Caspi et al., 2008; DeYoung et al., 2010). The role of COMT in relation to antisocial behaviour will be discussed in greater detail in Chapter 4.

Monoamine oxidase A (MAOA) is involved in the serotonergic, noradrenergic and dopaminergic pathways and breaks down neurotransmitters (Morley & Hall, 2003). MAOA has also been shown to be involved in antisocial behaviour (Denney, Koch, & Craig, 1999; Huang et al., 2004; Sabol, Hu, & Hamer, 1998). The MAOA gene is mapped on the short arm of X chromosome (Xp11.23-1140) (Lan et al., 1989) and is involved in the metabolism of neurotransmitters such as noradrenaline, serotonin and dopamine (Shih & Thompson, 1999). A 30-base repeat has been identified in the promotor region VNTR of the MAOA gene (Sabol et al., 1998) which consists of alleles comprising either 1, 2, 3, 3.5, 4 or 5 copies of a 30 bp (Denney et al., 1999; Huang et al., 2004; Sabol et al., 1998). The most common alleles are the 3-repeat (low activity) and 4-repeat (high activity) alleles (Denney et al., 1999; Guo, Ou, Roettger, & Shih, 2008; Sabol et al., 1998). The least common alleles are 3.5-repeat which is similar to 4-repeat in terms of being high activity. The 2-repeat is grouped with 3-repeat and considered as low activity (Kim-Cohen et al., 2006; Oreland, Nilsson, Damberg, & Hallman, 2007). Low activity MAOA alleles have been associated with high risk of impulsive aggression (Buckholtz & Meyer-Lindenberg, 2008). The 2-repeat allele variant has been associated with violent and delinquent behaviour (Beaver, Barnes, & Boutwell, 2014; Beaver et al., 2013; Guo et al., 2008). Deficiencies in MAOA lead to aggression in both animals and humans (Shih & Thompson, 1999).

A major limitation of candidate gene association studies is the focus on individual genes. It is now clear that multiple genes of small effect size influence complex phenotypes and hence there is a shift away from candidate gene studies towards the use of large-scale genome wide association studies (GWAS) (Stranger, Stahl, & Raj, 2011). Furthermore, genetic risks may interact with environmental risk (Plomin et al., 2013). This may explain some of the inconsistencies in the findings across studies (Ioannidis, 2003). Considering multiple genetic variants and environmental factors simultaneously may provide a better picture of the aetiology of antisocial behaviour (Rutter & Silberg, 2002). Indeed, there is an interplay between genes and environmental factors for emotional and behavioural traits which consists of two forms: gene-environment correlation (*r*GE) and gene-environment interaction (GxE). Gene-environment correlation (*r*GE) refers to the influence of genes on individual variations in *exposure* to adverse, and/or protective environments, and GxE refers to the effects of gene varying according to the environment, or put another way, the effects of the environment depending on genetic characteristics.

1.2.4.1.1 Gene-environment correlation

Environmental risk factors can be important for antisocial behaviour. Twin studies provide information about both shared and nonshared environmental influences. Shared environment refers to environmental factors that make siblings alike, whereas nonshared environment refers to environmental factors, which make siblings different from one another. Nonshared environmental variance includes any measurement error. In a meta-analysis, Rhee and Waldman (2002) found 16% shared environmental influence and 43% nonshared environmental influence on antisocial behaviour.

The *r*GE consists of three types: evocative, active and passive (Plomin, Defries, & Loehlin, 1977). Evocative *r*GE is the result of the behaviour performed by an individual based on their genotype, which *elicits* environmental response from others. Active *r*GE refers to the environment an individual *seeks* that reflects their genotype. Passive *r*GE refers to child's genotype inherited from their parents correlated with the environment the child is raised in. Individuals and their social environmental relationship can be uncovered by identifying the presence of passive *r*GE (Jaffee & Thoman, 2008). Parents play a significant role in their children's level of antisocial behaviour. For example, harsh parental discipline experienced by adolescents were strongly associated with greater externalising behaviours (Bender et al., 2007). Likewise, Larsson, Viding, Rijsdijk, and Plomin (2008) also found that parental negativity impacted on childhood antisocial behaviour through environmental mechanisms.

1.2.4.1.2 Gene-environment interaction

The GxE interaction examines whether environmental factors *moderate* the influence of genetic factors or, seen from another perspective, whether genetic factors moderate the effects of the environment on behaviour. Genetic influence on antisocial behaviour may vary for different environments. In a pioneering study using data from the Dunedin Multidisciplinary Health and Development study, Caspi et al. (2002) found that a polymorphism in the MAOA gene (low-activity) moderated the impact of early child maltreatment on development of antisocial behaviour in males. These effects have not always been replicated (Huizinga et al., 2006; Prichard, Mackinnon, Jorm, & Easteal, 2008). Nonetheless, a meta-analysis confirms the interaction effect across a number of studies (Byrd & Manuck, 2014).

1.3 Depression

Depression is a common psychiatric disorder among adolescents and young adults (Copeland, Shanahan, Costello, & Angold, 2009). According to DSM-5, Major Depressive Disorder (MDD) characterises discrete episodes of at least two-weeks duration involving changes in affect, cognition, and neurogenerative functions and inter-episode remissions. (American Psychaitric Association., 2013). Symptoms in the diagnostic criteria for MDD include depressed mood (e.g. feels sad, empty, hopeless), diminished interest or pleasure in activities in addition to the following symptoms: loss of weight, insomnia, fatigue, loss of energy, feeling of worthlessness, impaired concentration. The clinical diagnosis of MDD represents a categorical approach which implies whether a disorder is present or absent, this is based on specific, operationalised criteria with a set number of symptoms, occurring in specific frequency, intensity and duration. On the other hand, self-report depression represents a dimensional continuum, which varies from non-existence to severe which accounts for subject's own perception and evaluation of their depressive symptoms from a checklist.

1.3.1 Prevalence of depression

In the UK approximately 1.24 million people suffer from depression with an estimated £1.7 billion cost to the economy (McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008). By 2026 the estimated number of people with depression in England is projected to be 1.45 million (McCrone et al., 2008). Depression was ranked as the leading cause of disability in the Global Burden of Disease 2010 statistics (Murray et al., 2012). Depression is evident across the lifespan, emerging during childhood and adolescent years with increasing rates in adulthood (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001). MDD symptoms in adolescence have been shown to be a strong predictor of MDD in adulthood (Pine, Cohen, Cohen, & Brook, 1999). There is little difference in the prevalence of depression between boys and girls during pre-puberty (Egger & Angold, 2006). However, during adolescence the levels of depression increase mainly for girls which may be explained by social and biological changes (Cyranowski, Frank, Young, & Shear, 2000).

1.3.2 Measuring depression

Depression can be measured via different techniques including diagnostic interviews (unstructured, semi-structured and highly structured) (McClellan & Werry, 2000; Reitman et al., 1998; Roberts, Attkisson, & Rosenblatt, 1998). Major limitations of interview techniques are the cost and the time that are consumed with each interview which require trained interviewers with clinical expertise (King et al., 2001). Diagnostic interviews do not provide exact guidelines on how to determine clinically significant impairments required in diagnosis (Kessler, Avenevoli, & Merikangas, 2001). In addition, interviews do not usually contain normative data compared to rating scales (Reitman et al., 1998).

Depression can also be measured by rating scales with different informants (adolescents, parents, teachers) (American Academy of Child and Adolescent Psychiatry, 1998). Having multiple informants can be an advantage in capturing different profiles of symptoms in different settings. However, adults may not be aware of adolescent's depression (Cantwell, Lewinsohn, Rohde, & Seeley, 1997), which can lead to low agreement between different informants (Sourander, Helstela, & Helenius, 1999; Verhulst, Van Der Ende, Ferdinand, & Kasius, 1997). Thus, the most valid informants are considered to be adolescents themselves (Hankin & Abramson, 1999). Rating scales provide an advantage over interviews in enabling comparisons between an adolescent's level of depression and a reference group of the same age and gender (Achenbach, 1991). Nonetheless, these methods also have their limitations as these cannot be used as diagnostic instruments which rely on a person's own perception and evaluation of depressive symptoms (Kessler et al., 2001). However, some studies have shown that self-report measures are approximately equivalent to clinically diagnosed disorders (Boyle et al., 1997; Lasa, Ayuso-Mateos, Vazquez-Barquero, Diez-Manrique, & Dowrick, 2000; Morgan & Cauce, 1999). The self-report measures have also been shown to be persistent and associated with significant psychosocial impairment in adolescence and adulthood (Ferdinand, Verhulst, & Wiznitzer, 1995; Glied & Pine, 2002; Twenge & Nolen-Hoeksema, 2002). There is also evidence that adolescents who scored high on a depression questionnaire did not differ significantly on psychosocial dysfunction compared to adolescents meeting diagnostic criteria for depression (Gotlib, Lewinsohn, & Seeley, 1995). The three studies in this thesis will use the short version of Mood and Feeling

Questionnaire (SMFQ) consisting of 13 item which address the symptoms of major depression included in DSM-5 (American Psychaitric Association., 2013). The SMFQ has been adopted in a number of self-report studies, and has good psychometric properties. The scores from SMFQ show a unifactorial structure, reflecting the core construct of depression (Messer et al., 1995).

1.3.3 Sex difference in depression

Sex differences for depression begin to emerge around the time of adolescence (Hankin, Mermelstein, & Roesch, 2007). Across a seven-wave study with respondents interviewed at two-year interval (from childhood to young adulthood), Dekker et al. (2007) found sex differences in depressive problems in terms of level, shape and timing of onset. In adolescence, girls with deviant depressive symptoms showed an increase in their symptoms over time whereas in boys a decreasing trajectory of depressive symptom was found. Following puberty in adolescence, a higher prevalence of depression was found among girls (2:1) compared to boys (Hyde, Mezulis, & Abramson, 2008). This is consistent across a number of studies showing higher rates of depression among girls (Ge, Conger, & Elder, 2001; Hankin, 2009).

1.3.4 Aetiology of depression

1.3.4.1 Genetic

Depression is highly heritable, with estimates ranging between 30-50%, increasing from childhood to adulthood (Rice, Harold, & Thapar, 2002). Heritability rates of adolescent depression was reported to be similar to adult depression (Thapar & Rice, 2006). In a longitudinal twin study using G1219 data from community sample over three time points (adolescence to young adulthood), Lau, Rijsdijk, and Eley (2006) found moderate genetic influence across all three time points which accounted for approximately half the phenotypic variance. A recent systematic review of seven longitudinal twin studies reported stability of genetic factors in depression symptoms across adolescence from five of the studies (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2016).

At the molecular level, candidate genes across multiple pathways have been found to be associated with depression. A functional variant (C825T) within the G-protein β3 (GNβ3) has been linked to depression (Fang et al., 2015). GNβ3 gene acts as a secondary messenger of the serotonergic pathway during signal transductions (Cabrera-Vera et al., 2003; Lopez-Leon et al., 2008). The T allele within the GNβ3 C825T contributes to deletion of 41 amino acids which result in alterations in cellular signal transduction and ion transport. In a recent meta-analysis of case-control studies, nine studies revealed that T allele of the GNβ3 (C825T) gene was associated with increased susceptibility to depression among Asians not Caucasians (Fang et al., 2015).

Among the neurochemicals, the 5HTTLPR polymorphism has been studied intensively in relation to depression, which is part of the serotonergic variants (Lesch et al., 1994). A meta-analysis reported an association between depression and the S allele of 5HTTLPR (Lopez-Leon et al., 2008; Lotrich & Pollock, 2004). Serotonin receptor genes have also been associated with depression. For example, the serotonin receptor 1A gene (HTR_{1A}) (Lopez-Leon et al., 2008) and serotonin receptor 1B gene (HTR_{1B}) have both been associated with depression (Holmans et al., 2004). In addition, serotonin receptor 2A (HTR_{2A}) has been associated with depression (Oquendo & Mann, 2001) and MDD (Christiansen et al., 2007). However, meta-analyses have reported results with no association between HTR_{2A} with depression (Anguelova, Benkelfat, & Turecki, 2003; Lopez-Leon et al., 2008).

Furthermore, high activity MAOA has been associated with depression (Du et al., 2002). Females with MDD were found to have an increased frequency of the 4-repeat allele of MAOA (Yu et al., 2005). This has been replicated in individuals at risk of MDD showing an increased frequency of the high activity 4-repeat allele (Lung, Tzeng, Huang, & Lee, 2011; Rivera et al., 2009). Low activity MAOA has been commonly associated with depressive symptomatology but reports are conflicting (Aklillu, Karlsson, Zachrisson, Ozdemir, & Agren, 2009; Brummett et al., 2007; Doornbos et al., 2009). Other polymorphisms including Val-allele in the COMT gene has been associated with risk for MDD (Massat et al., 2005). Further details on the association between COMT and depression will be discussed in Chapter 4.

1.3.4.1.1 Gene-environment correlation

Stressful life events can trigger the onset of depression, for example, experience of neglect, abuse and parental loss have been shown to be associated with later depression (Heim & Nemeroff, 2001). Stress has a significant influence on depressive symptoms (Ge et al., 2001). Some of the common stressors affecting depression include bullying and negative family relationships (Restifo & Bogels, 2009; Rueter, Scaramella, Wallace, & Conger, 1999). For example, adolescents experiencing harsh parental discipline experienced greater depression (Bender et al., 2007). A longitudinal survey showed that mothers’ use of physical punishment was a predictor of children’s depressive symptoms (Eamon, 2002).

Besides stress, negative life events have also been found in depressed individuals (Ge, Natsuaki, Neiderhiser, & Reiss, 2009; Hammen, 2005; Kendler, Karkowski, & Prescott, 1999; Lewinsohn, Allen, Seeley, & Gotlib, 1999; Paykel, 2003; Rijsdijk et al., 2001). Negative life events are sometimes sub-divided into dependent (events such as interpersonal conflicts induced by the individual) and independent life events (events such as death of a spouse not in control of the individual) (Brown & Harris, 1978). Dependent life events have been found to have stronger effects on risk of onset of depression compared to independent life events (Kendler et al., 1999; Kercher, Rapee, & Schniering, 2009). This is further reinforced by a study showing reciprocal association between negative life events and depressive symptoms (Wichers et al., 2012).

The association of *r*GE and depression is well documented in the literature which show that environmental factors (parenting, stressful life events, negative life events) that partly influence an individual's psychopathology is in fact influenced by heritable characteristics (Jaffee & Thoman, 2008; Kendler & Baker, 2007). These effects have been found in bivariate twin studies of children and adolescents showing support for the role of shared genetic influence on the association between putative environmental measures and depression (Neiderhiser, Reiss, Hetherington, & Plomin, 1999; Pike, McGuire, Hetherington, Reiss, & Plomin, 1996). Rice, Lewis, Harold, and Thapar (2013) examined the role of passive *r*GE in relation to depression, family life events and parental positivity in 865 families. They demonstrated that environmental factors contributed toward the intergenerational transmission of depressive symptoms whereby parents depressive symptoms were associated with their children's reduced positivity.

1.3.4.1.2 Gene-environment interaction

The GxE effects are also evident in depression. For example, in the presence of adverse life stressors or maltreatment, a variant of 5HTTLPR has been associated with risk of depression (Caspi et al., 2003; Uher & McGuffin, 2010). Caspi et al. (2003) found that 5HTTLPR moderated the association between stressful life events and the development of depression. The carriers of one or two copies of the S allele showed more depressive symptoms, diagnosable depression and suicidality when exposed to stressful life events compared to L allele carriers. Other studies have also found carriers of the S allele were at a greater risk for depression when exposed to stress (Cervilla et al., 2007; Kaufman et al., 2006; Wilhelm et al., 2006). A meta-analysis of 51 studies confirmed that the relationship between depression and stress was moderated by 5HTTLPR, with the S allele of 5HTTLPR associated with risk for depression (Karg, Burmeister, Shedden, & Sen, 2011). Besides stress, Kaufman et al. (2004) found that maltreated children with the S alleles experienced a high level of depression.

In addition to the S and L alleles of 5HTTLPR, an additional functional single nucleotide polymorphism has been detected (A/G, rs25531) in the upstream promotor region of 5HTTLPR which has a minor G and a major A allele that is present in both L and the S allele (Kraft et al., 2005). Single-base substitution (A to G) within the L allele creates the L_A and L_G alleles. Hu et al. (2005) found that L_G alleles perform in a similar way to S alleles. This gene subdivides the S allele (S_A, S_G) and the L allele (L_A, L_G) located in the upstream of the promotor region of 5HTTLPR, and has a regulatory role. Zalsman, Brent, and Weersing (2006) investigated the genes x stressful life events interaction with regards to depression. Lower expressing alleles (L_G, S) predicted depression independently and increased impact of life events on the severity of depression in a Caucasian sample, in comparison to higher expressing genes (L_A). In total, around 10% of the L alleles were in the L_G low expressing alleles that were previously considered as high-expressing genes.

There are contradictory findings on GxE interaction between depression and MAOA gene. Some studies have found no association between MAOA and child maltreatment (Caspi et al., 2002) and between MAOA and negative family events (Eley et al., 2004). On the other hand, two studies have found the opposite effect. Symptoms of depression were predicted by the interaction of low activity (3-repeat) allele of MAOA and child maltreatment (Cicchetti, Rogosch, & Sturge-Apple, 2007). Beach et al. (2010) found that a high activity MAOA genotype predisposed children to MDD in the context of maltreatment. Other gene polymorphisms involved in the stress hormone system have also been implicated in depression. For example, Bradley et al. (2008) found an interaction of CRH Type 1 receptor (CRHR1) gene and child abuse predicting depressive symptoms.

1.4 Comorbidity

Antisocial behaviour and depression are comorbid above chance level (Angold, Costello, & Erkanli, 1999). Angold et al. (1999) conducted a meta-analysis of epidemiological studies from the general population on the association between depression and CD in children and adolescents, which reported a median odds-ratio of 6.6 for the association. Although, CD was almost seven times more common in those diagnosed with depression than those without. This demonstrates a strong link between antisocial behaviour and depression in the general population.

Comorbidity between antisocial behaviour and depression is associated with a number of negative outcomes including increases risk for suicide (Marmorstein & Iacono, 2004), developing substance abuse (Brenner & Beauchaine, 2011), involvement with deviant peers (Ingoldsby, Kohl, McMahon, & Lengua, 2006), poorer treatment response, poorer outcome and greater impairment (Keiley, Lofthouse, Bates, Dodge, & Pettit, 2003; Youngstrom, Findling, & Calabrese, 2003). Ezpeleta, Domenech, and Angold (2006) compared clinical samples of CD combined with depression and pure CD. The former group showed greater anger, and reported higher somatic complaints and resentment in contrast to the latter group. The comorbidity of both CD and depression across the groups contributed to higher levels of emotional and functional problems.

At the clinical level, the risk for developing CD was extremely high in individuals with depression (Biederman, Faraone, Mick, & Lelon, 1995). The converse association was also found in one study showing that approximately 30% of children diagnosed with MDD also met criteria for CD; whilst 50% of children with CD meeting criteria for MDD (Greene et al., 2002). Similarly, there is a high degree of comorbidity between ODD and depression (Kelsberg & St Anna, 2006). When considering studies of clinical populations, it is important to note that referral bias may partially account for the high number of patients displaying comorbidity (Caron & Rutter, 1991). Consequently, there is a need to address comorbidity in the general population. In a community study of adolescent boys and girls, Rowe, Maughan, and Eley (2006) found that depressed mood was independently predicted by oppositionality whereas life events mediated the influence of delinquency on depressed mood.

1.4.1 Sex difference in comorbidity

The comorbidity between depression and antisocial behaviour can also vary depending on the sex of the individual. Sex difference has been reported in the co-occurring depressive symptoms and delinquent behaviours in children and adolescence. Wiesner (2003) using longitudinal data with four time-points (at 6 month intervals), investigated the reciprocal association between depressed mood and delinquency over time. Unidirectional associations were found between delinquency and depressive symptoms among boys in that greater delinquency was associated with higher levels of depressive symptoms. For girls, bidirectional effects were found with a stronger and more consistent pattern of association between the two behaviour problems. Similarly, Wiesner and Kim (2006) reported heterogeneity and gender difference in depressive symptoms and delinquent behaviour in a longitudinal study over a two-year period in middle adolescence. Higher overlap between the two behaviours was found among girls compared to boys (50% vs. 25%). In boys, depressive symptoms were predicted by delinquent behaviour rather than vice versa, whereas for girls both directions of effects were present showing mutual effect. Chen and Simons-Morton (2009) also found that adolescents high in conduct problems were also high on depression, however the overall trend was equally similar in boys and girls.

1.4.2 Diagnostic criteria overlap

At a diagnostic level, antisocial behaviour and depression show overlaps in the diagnostic criteria. For example, in a clinic study of referred boys, Greene et al. (2002) found that 30% of those diagnosed with MDD also met criteria for conduct problems; 50% of those who were diagnosed with conduct problems also met criteria for MDD. The non-specific symptoms that are shared may generate an overlap in diagnosis for both. Irritability is a symptom of depression and ODD, and there is more evidence for overlap between ODD and depression than with CD (Burke, Loeber, Lahey, & Rathouz, 2005; Rowe et al., 2006). However, one study found that removing the overlapping symptoms did not remove the overlap between depression and ODD (Biederman et al., 1995).

1.4.3 Aetiology of comorbidity

The aetiological nature of the association between antisocial behaviour and depression is unclear. A number of common factors may increase the risk for both behaviour problems, or each problem may be a representative variation in expression of a single underlying trait. There may also be causal effects between both traits or common psychosocial risk factors (Lewinsohn, Gotlib, & Seeley, 1995). There may also be different manifestation of the same underlying disorder (Caron & Rutter, 1991). It may also be due to common developmental pathways including genetic and environmental factors.

1.4.3.1 Common risk factors

The comorbidity between antisocial behaviour and depression can be explained by the presence of common risk factors (Wolff & Ollendick, 2006). Antecedent factors may lead to comorbidity by two methods. Firstly, risk factor for one disorder may be the same for the other disorder, secondly, there may be correlation between the risk factors for the two disorders (Caron & Rutter, 1991). A number of research studies have reported inter-correlation and overlap between risk factors for antisocial behaviour and depression (Fergusson, Lynskey, & Horwood, 1996). Negative emotionality acts as a risk factor for both antisocial behaviour and depression (Eisenberg, Fabes, Guthrie, & Reiser, 2000). Social contextual model of parental influence and coercive theory claim that disruptive parenting generates and maintains behavioural problems and are also associated with delinquent peers which in turn contributes to additional novel behavioural problems (Scaramella, Conger, Spoth, & Simons, 2002). For example, exposure to domestic violence and child maltreatment has been reported to contribute to increased levels of externalising problems and also affecting internalising problems (Davies & Windle, 2001). These shared risk factors may account for the strong association between antisocial behaviour and depression. On the other side of spectrum, studies identifying shared risk factors fail to identify environmental or socio-contextual influences that account for antisocial behaviour and depression covariation (Beyers & Loeber, 2003).

1.4.3.2 Genetic

In addition to showing that both antisocial behaviour and depression are heritable, there is evidence that the same genetic variance is shared between the two (O'Connor, McGuire, Reiss, Hetherington, & Plomin, 1998; O'Connor, Neiderhiser, Reiss, Hetherington, & Plomin, 1998). In a sample of 720 same-sex adolescent twins aged between 10 to 18 years, overlap between antisocial behaviour and depression was reported to be partially genetically mediated in that 45% of covariation between antisocial behaviour and depression was attributable to shared genetic effects, with 30% attributable to shared environmental effects and 25% to the effects of nonshared environment (O'Connor, McGuire, et al., 1998). Rowe, Rijsdijk, Maughan, Hosang, and Eley (2008) found a strong genetic overlap between antisocial subscales (delinquency, oppositionality and physical aggression) and depressed mood. In a separate study, data from the Colorado Twin Registry reported a significant genetic correlation between MDD and CD (Subbarao et al., 2008).

1.4.3.2.1 Gene-environment correlation

Twin studies have reported covariation between antisocial behaviour and depression attributable to shared environmental effects (30%) and nonshared environmental effects (25%) (O'Connor, McGuire, et al., 1998). Environmental effects also play a pertinent role in both antisocial behaviour and depression. Hipwell et al. (2008) studied longitudinal association between parental behaviour (e.g. harsh punishment and warmth) on conduct problems and depressed mood in 2,451 girls from age 7 to 12 years. A reciprocal relationship was found between parental behaviour and child behaviour in that harsh punishment and low warmth from parents were associated with conduct problem and depressed mood in girls, also conduct problems and depressed mood in girls predicted a reduction in warmth and an increase in harsh punishment from parents. A lifetime history of harsh maternal and paternal discipline in adolescence has been associated with depression and externalising behaviour (Bender et al., 2007).

The genetic effects shared between antisocial behaviour and depressed mood may represent *r*GE. For example, there might be an evocative *r*GE whereby a child's genetically influenced depressed mood may evoke an environmental response which results in antisocial behaviour (Plomin et al., 2013). Children with low mood may show failures in academic work which evokes a response from others (e.g. teachers treating the child as one of the 'bad kids') and contributes to antisocial behaviour. Likewise, genetically influenced antisocial behaviour may evoke depressogenic effect from the environment. The association could also be explained by active *r*GE, whereby children or young adults seek or create environments correlated with their genetic propensities. For instance, children who are antisocial may actively seek out poorly behaved peers, which may result in poor behaviour and punishment, which could contribute to depressed mood. Likewise, children who are depressed might face peer rejection, which in turn contributes to antisocial behaviour. The strong genetic effects across time does not rule out the possibility that environmental influences are influential in the association between antisocial behaviour and depressed mood.

1.4.3.2.2 Gene-environment interaction

The GxE has been found for antisocial behaviour and depression. The environmental factors involved in antisocial behaviour include family circumstances (e.g. income, socio-economic status) (Button, Scourfield, Martin, Purcell, & McGuffin, 2005; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Caspi et al., 2002; Foley et al., 2004; Jaffee et al., 2005) and stressful life events for depression (Cadoret et al., 1996; Caspi et al., 2003; Eley et al., 2004; Kaufman et al., 2004; Silberg, Rutter, Neale, & Eaves, 2001). In a study conducted by Feinberg, Button, Neiderhiser, Reiss, and Hetherington (2007), environmental factors including parental negativity and parental warmth were assessed as moderators on genetic factors in accounting for variance in depression and antisocial behaviour. This study found that both parental negativity and parental warmth moderated the influence of genetic factors on antisocial behaviour but not on depression. The genetic effects on antisocial behaviour were at peak with high parental negativity and low levels of parental warmth. However, the parental effects are not salient factors for depression as common types of environmental factors include stressful life events.

1.5 Models of development over time

Three main developmental theories have been proposed to explain the association between antisocial behaviour and depression including the failure model (Patterson & Capaldi, 1990), the acting out model (Overbeek, Vollebergh, Meeus, Engels, & Luijpers, 2001) and the mutual reinforcement model (Wolff & Ollendick, 2006). This section will discuss in depth the different models with evidence from clinical and general population studies.

1.5.1 Failure model

According to the failure model, antisocial behaviour predicts depressed mood (Patterson & Capaldi, 1990). The model posits that both aggressive and disruptive behaviour contribute towards social isolation and peer rejection which in turn results in depression. Similarly, interactions with teachers and parents (e.g. conflicts) result in failure at an academic level which in turn leads to depression. Both of these negative reactions resulting from the lack of competence academically and rejection from peers contribute towards pervasive failures that consequently lead to depression (Capaldi & Stoolmiller, 1999). A number of studies are in line with this model (Moffitt & Caspi, 2001; Vieno, Kiesner, Pastore, & Santinello, 2008). Capaldi (1992) found that boys high in CD at Grade 6 (age 12 years) reported increased depressed mood symptoms at Grade 8 (age 14 years). Longitudinal studies have also reported early antisocial behaviour predicting later depressed mood (Copeland et al., 2009; Kim, Conger, Elder, & Lorenz, 2003; Kosterman et al., 2010; Mason et al., 2004; McCarty et al., 2009).

Besides CD predicting depression, ODD has also been found to be a strong predictor of depression and CD during the pre-adolescent stage in girls (Angold et al., 1999; Boylan, Vaillancourt, Boyle, & Szatmari, 2007). Deviant peer affiliation has been found to result in an increase in externalising behaviour which in turn contributed to negative consequences resulting in depression longitudinally (Fergusson, Wanner, Vitaro, Horwood, & Swain-Campbell, 2003). Copeland et al. (2009) conducted a longitudinal study from adolescence to young adulthood and found that depression was predicted by ODD but that depression did not predict ODD. This direction of association has been identified in a review of clinical and community studies (Boylan et al., 2007).

The path from CD to depression may operate via a number of developmental failures with potential mediating variables including familial, social and academic dimensions (Capaldi, 1992; Patterson & Capaldi, 1990). Adolescents and young adults with delinquency at an earlier time point may experience negative life events which may act as strong triggers for depressed mood later on (Rowe et al., 2006). There is some evidence that stressful life events mediate the relationship between externalising and internalising problems from early childhood to late adolescence (Timmermans, van Lier, & Koot, 2009).

Longitudinal studies have reported comorbidity between antisocial behaviour and depressed mood over time. A 10-year longitudinal study of clinically referred boys from childhood through to adolescence examined annual changes in depression, anxiety, attention hyperactivity disorder (ADHD), ODD and CD (Burke et al., 2005). This study revealed that depression was predicted from ODD in one year following referral. The symptoms of ODD can also predict depression in later adulthood (Copeland et al., 2009). A study by Wertz et al. (2015) followed participants from childhood to preadolescence (age 5 to 12 years) examining the role of negative experiences including bullying victimisation, academic difficulties and maternal dissatisfaction in the association between early externalising problems and later internalising symptoms. Negative experiences partially mediated this association in phenotypic analyses. Behavioural genetic analyses also showed that genetic effects specific to age 5 externalising problems influenced internalising problems at age 12. Thus, genetic influences from early externalising problems predicted later internalising problems which indicate that comorbidity is established in early childhood.

1.5.2 Acting out model

In direct comparison to the failure model, the acting out model postulates that depression leads to antisocial behaviour (Carlson & Cantwell, 1980). Here the externalising problem behaviours are displayed which uncover the underlying depressive feelings (Carlson & Cantwell, 1980). The acting out behaviour accompanies the depressive feelings which contribute to masked depression (Benamos, 1992). Hence, depression is masked by engaging in antisocial behaviour and acting out these activities. Consistent with this model, Kofler et al. (2011) found that early symptoms of depression predicted changes in delinquent behaviour over time from age 12 to 17 years. Hence, depression is a major risk factor for delinquency in girls (Wiesner, 2003).

1.5.3 Mutual reinforcement model

A reciprocal relationship may account for the association between antisocial behaviour and depression. This model combines elements of the failure and acting out model to account for the mutual association between antisocial behaviour and depression (Gilliom & Shaw, 2004; Measelle, Slice, & Hogansen, 2006). Longitudinal studies have found reciprocal associations over time. For example, changes between internalising and externalising behaviour have been shown to be positive over time from the age of 2 to 6 years in boys (Gilliom & Shaw, 2004) and from kindergarten to seventh grade (Keiley, Bates, Dodge, & Pettit, 2000), as well as females (Measelle et al., 2006). Beyers and Loeber (2003) also conducted a longitudinal study to examine the concurrent and longitudinal association between delinquency and depressed mood. Reciprocal association was found between depressed mood and delinquency while controlling for common risk factors. The reciprocal associations between delinquent behaviour and depressive symptoms has been shown to differ by gender, for example Wiesner (2003) found a bidirectional effect in adolescent girls but a unidirectional effect in adolescent boys.

1.6 Rationale and thesis outline

The overall aim of this thesis is to investigate the association between antisocial behaviour and depressed mood over time within the general population at phenotypic, behavioural genetic and molecular genetic levels. Previous research has focussed mainly on cross-sectional analyses at a single time point. For example, Rowe et al. (2006) used a single wave from G1219 dataset focussing on the adolescent stage (modal age = 15) and found that depressed mood was associated with oppositionality and delinquency. A follow up study by Rowe et al. (2008) used the same wave of data for genetic analyses which showed that the correlation between depressed mood and antisocial behaviour subtypes were largely accounted for by genetic overlap. There is limited research that address the longitudinal overlap between antisocial behaviour and depressed mood. Our study extended the cross-sectional analysis of the G1219 study reported by Rowe et al. (2006), by testing longitudinal associations using the addition of later waves of the data collection that have more recently become available (three further contact points with mean ages 15, 17 and 20 years, supplementing the existing data from 2006). The studies conducted in this thesis has the advantage of using various methods including phenotypic, genetic and molecular genetic to investigate the overlap. This provides analysis of the overlap using different methodologies, moving beyond one standard method.

The thesis uses data from the Genesis 12-19 study of twins and siblings, which represents a large UK community sample, from which data have been collected at five time points. Chapter 2 will address the first aim of this thesis, which focusses on the phenotypic association between antisocial behaviour subtypes and depressed mood from adolescence to adulthood. Using structural equation modelling, this study will assess the directional effects from one trait to another across time, which will inform the different developmental models (failure model, acting out model and reinforcement model). Chapter 3 will cover the second aim of this thesis using behavioural genetic analyses to assess the genetic and environmental association between antisocial behaviour and depressed mood over time. This study focusses on the influences underlying the association between the phenotypes over time, both new and shared genetic and environmental influences. Chapter 4 will cover the third aim of the thesis by investigating some candidate genes that might be involved in both antisocial behaviour and depressed mood and therefore contribute to their comorbidity.

1.7 Sample information

The data for this study is from wave 2, 3 and 4 of the G1219 longitudinal studies. The G1219 is well suited for the current thesis as it represents a nation-wide study of twins and siblings growing up in the UK. The inclusion of sibling pairs provides an increased power for detection of environmental effects that are common to family members, in additional to the advantage of generalisation. Sibling pairs originated from the GENESiS study (Sham et al., 2000) (see Figure 1.1) which comprised approximately 40,000 adults of whom approximately 9,000 had indicated that they had children living with them (McAdams et al., 2013). Informed consent was obtained from parents / guardians of all adolescents under 16 years and from adolescents themselves when aged 16 years and over. Ethical approval for different stages of this study has been provided by the Research Ethics Committees of the Institute of Psychiatry, South London and Maudsley NHS Trust, and Goldsmiths, University of London.

Initial contact for data collection for the G1219 study began in 1999 in three stages: GENESiS families (contacted during 1999-2000), twins born in 1985 (contacted during 2000), and twins born in 1986-1988 (contacted during 2001). At wave 1, there was a total of 3,640 adolescents from 1,820 families with age range 12-19 years (mean = 14 years; 52% female). At wave 2, data collection was mainly on twins and siblings, 75% from wave 1 participated, total 2,651 adolescents from 1,372 families (mean = 15 years; 56% female). At wave 3, data were collected from 1,778 adolescents from 913 families (mean = 17 years; 60% female). At wave 4, a total of 1,556 individuals from 896 families took part in the study (mean = 20 years; 61% female).

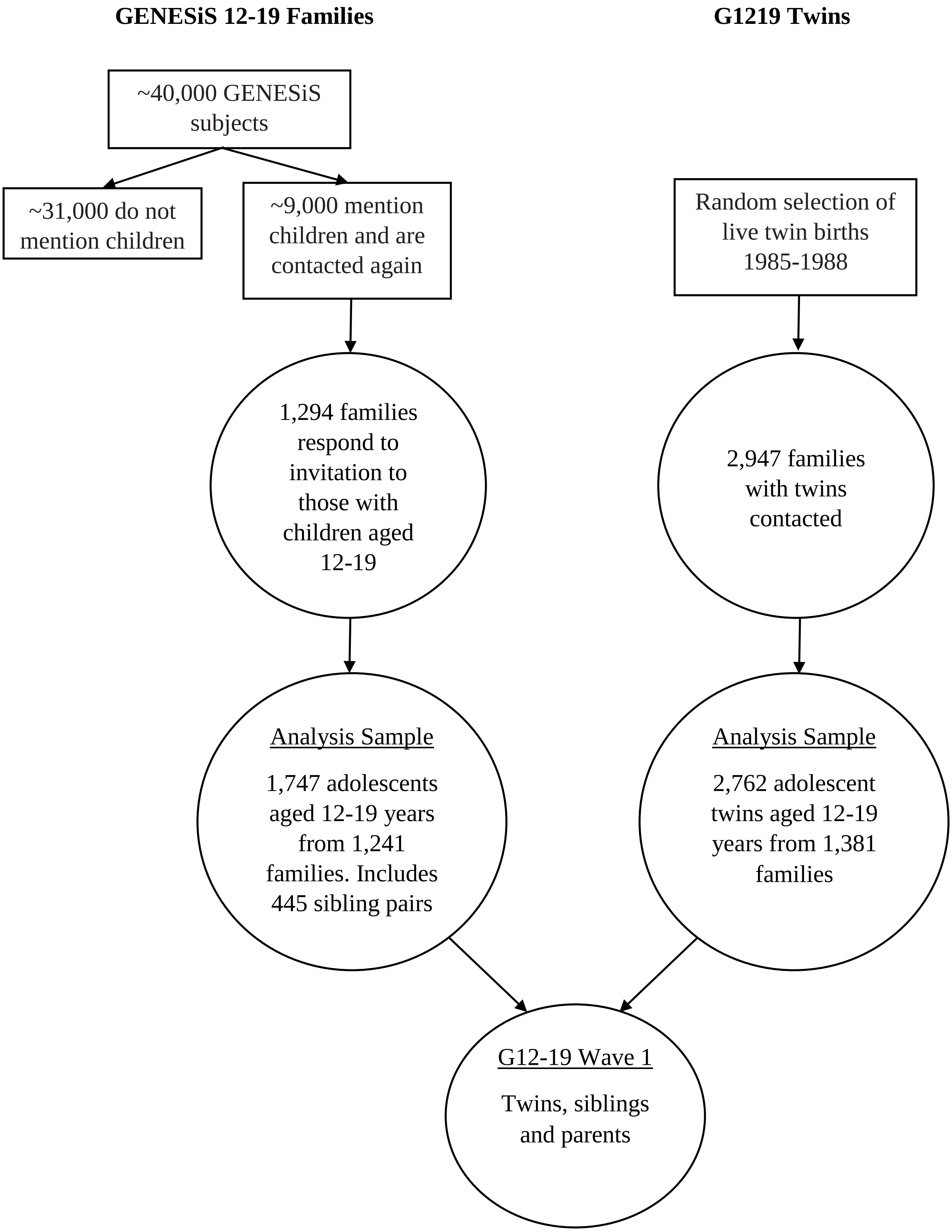

Figure 1.1 Sample recruitment in the G1219 study (McAdams et al., 2013)

Chapter 2 Antisocial behaviour subtypes and depressed mood: Longitudinal associations from adolescence to adulthood

2.1 Overview

This chapter investigates the longitudinal association between antisocial behaviour subscales (oppositionality and delinquency) and depressed mood across three time points. Data were drawn from the G1219 twin and sibling sample. Antisocial behaviour and depressed mood were assessed using self-report measures, collected at three time points (mean ages: 15, 17 and 20 years). The association between antisocial behaviour and depression result from three pathways (a) antisocial behaviour leading to depressed mood; (b) depressed mood leading to antisocial behaviour; (c) antisocial behaviour and depressed mood reciprocally reinforce each other and lead to increases in the other. Structural equation models were used to run autoregressive cross-lagged models. Results confirmed strong cross-sectional associations between traits at each time point. Early depressed mood was significantly associated with later oppositionality and this was a better predictor of later oppositionality than early oppositionality was of later depressed mood. These findings provide support for the acting out model. However, depressed mood did not predict delinquency or oppositionality which contradict the failure model. Further work on the cross-trait association at a genetic level is imperative to establish the mechanisms linking depressed mood and oppositionality.

2.2 Introduction

As noted in Chapter 1, antisocial behaviour and depression are associated with median odds-ratio of 6.6. This association was of a similar strength to the well-documented link between depression and anxiety disorders (Angold et al., 1999). A longitudinal study of clinic-referred boys aged between 7 to 12 years at initial stage who were annually assessed until age 18 showed strong prediction of depression from ODD (Burke et al., 2005). Despite the strong associations identified across different studies, the mechanisms underlying this association are not fully understood. Shared risk factors (e.g. biological and socio-contextual factors) between antisocial behaviour and depression may underlie the comorbidity (Caron & Rutter, 1991; Wolff & Ollendick, 2006). It is also possible that high levels of one form of psychopathology increase risk for developing the other at a later time. There are three developmental models of this sort: the failure model (Patterson & Capaldi, 1990), the acting out model (Overbeek et al., 2001), and the mutual reinforcement model (Wolff & Ollendick, 2006).

The failure model proposes that antisocial behaviour may act as a precursor to depressed mood via failures in social situations, which in turn contribute to depression (Overbeek et al., 2001; Patterson & Capaldi, 1990). This model has been supported by longitudinal studies, for example, Capaldi (1992) found that conduct problems at Grade 6 (12 years old) predicted high rates of depression at Grade 8 (14 years old). Van der Giessen et al. (2013) examined early aggressive behaviour and later depressive symptoms annually from 12 to 15 years. Early aggressive behaviour predicted later depressive symptoms. These effects have been found from different age groups; for example from childhood to adolescence (Hipwell et al., 2008) and adulthood (Copeland et al., 2009; Kosterman et al., 2010). A similar pattern has been found in community samples; for example the national comorbidity survey study found that CD was more likely to occur before co-morbid depression, and those with either active or remitted CD were at a greater risk for developing depression later in life (Nock, Kazdin, Hiripi, & Kessler, 2006). There are a number of potential mediating variables on the path from CD to depression including familial, social and academic dimensions (Capaldi, 1992; Patterson & Capaldi, 1990). Rowe et al. (2006) found that dependent negative life events mediated the relationship between delinquency and depressed mood. Other mechanisms involved in the association from internalising problems to externalising problems include other negative experiences such as bullying victimisation and academic failures (Wertz et al., 2015).

Conversely, the acting out model posits that antisocial behaviour develops from depressed mood (Overbeek et al., 2001) as irritability symptoms associated with depression become severe and contribute to acting out behaviours (Wolff & Ollendick, 2006). In line with this model, Kofler et al. (2011) found that early symptoms of depression predicted changes in delinquent behaviour over time from age 12 to 17 years. These effects have also been found from adolescence to adulthood (Capaldi & Stoolmiller, 1999; Ritakallio et al., 2008).

The mutual reinforcement model combines elements of the failure and acting out models to specify reciprocal relationships between antisocial behaviour and depressed mood (Gilliom & Shaw, 2004; Measelle et al., 2006). For example, Beyers and Loeber (2003) examined both concurrent and longitudinal associations between delinquency and depressed mood, finding concurrent reciprocal associations between both traits while controlling for common risk factors. However, the associations were not symmetrical and there was a stronger association between earlier depressed mood and later delinquency than between early delinquency and later depressed mood.

Antisocial behaviour is a heterogeneous construct as discussed in Chapter 1. Thus, the mechanisms linking it to depressed mood may vary depending upon the subtype of antisocial behaviour in question. Antisocial behaviour can be subdivided in different ways. For example, the DSM-5 (American Psychaitric Association., 2013) distinguishes CD, which involves aggression towards people or animals, destruction of property, or theft and deceit, from ODD, which involves problems of emotional dysregulation (i.e. angry / irritable mood) and headstrongness (e.g., defiance). Factor analytic research additionally supports heterogeneity within CD (Frick et al., 1993). Subtypes of CD including aggressive behaviour and non-physically aggressive delinquent behaviour have been identified (Tackett et al., 2003). There are developmental differences between each subtype. For example, physical aggression shows a stable decline from childhood to adulthood and this behaviour problem may be resolved by early adulthood in some cases (Bongers, Koot, van der Ende, & Verhulst, 2003; Stanger et al., 1997). In contrast, non-aggressive delinquent behaviour is much less frequent in childhood, and increase throughout adolescence before decreasing in adulthood (Burt & Neiderhiser, 2009; Sampson & Laub, 2003; Stanger et al., 1997).

Associations between antisocial behaviour and depressed mood may differ for different subtypes of antisocial behaviour. For example, Rowe et al. (2006) found that delinquency and oppositionality were independently associated with depressed mood while physical aggression was not. Previous longitudinal studies have not explicitly tested whether there are different links between the different subtypes of antisocial behaviour and depressed mood over time. Copeland et al. (2009) studied longitudinal predictions from childhood to young adulthood between depression and oppositionality in the Great Smokey Mountains study. Strikingly, early oppositionality predicted depression in adulthood. Oppositionality consists of features of irritability, which has been associated with depression (Stringaris & Goodman, 2009a, 2009b).

2.2.1 Aims

This study aimed to examine the associations between depressed mood and two subscales of antisocial behaviour (delinquency and oppositionality). These dimensions of antisocial behaviour have previously been shown to be associated with depressed mood from adolescence to adulthood. Our study extended the cross-sectional analysis of the G1219 study reported by Rowe et al. (2006), by testing longitudinal associations using the addition of later waves of the data collection that have more recently become available. In line with the failure model, we hypothesised that oppositionality and delinquency will predict depressed mood. In line with the acting out model, we hypothesised that depressed mood predicts oppositionality and delinquency. We applied a series of autoregressive cross-lagged structural equation models to test these hypothesised relationships between antisocial behaviour subscales and depressed mood over time. Cross-lagged models have been used widely in developmental research for assessment of bidirectional relations between traits (Defoe, Farrington, & Loeber, 2013).

2.3 Method

2.3.1 Sample

The G1219 study is a large community-based sample for which data have been collected over 5 waves. Our analyses focus on waves 2, 3 and 4; hereon referred to as time points 1, 2 and 3 respectively, for ease of presentation. At time 1 the response sample was 2,651 (mean age = 15 years; range = 12 - 21 years); at time point 2, the response sample was 1,597 (mean age = 17 years; range = 15 - 23 years); and at time 3 there were 1,556 respondents (mean age = 20 years; range = 18 - 27 years) respectively. The percentages of female participants were 52%, 56% and 60% for time points 1, 2 and 3 respectively.

Informed consent was obtained from parents/guardian of all adolescents under 16 and from adolescents themselves when 16 and over. Full details of the G1219 (Genesis 12-19) study sample can be found in Chapter 1 and elsewhere (McAdams et al., 2013).

Attrition was examined to determine whether participants who dropped out at time 2 and 3 differed from those who stayed in the study. Participants with higher oppositionality at earlier time points showed a greater tendency to drop out of the study. The odds ratio (OR) for a 1 standard deviation (SD) increase in oppositionality at time 1 predicted drop out at time 2 (OR = 1.25, 95% Confidence Interval (CI) = 1.04 - 1.22, p<.001), also a 1 SD increase in oppositionality at time 2 predicted drop out at time 3 (OR = 1.44, 95% CI = 1.29 – 1.61, p<.001). The OR for a 1 SD increase in delinquency at time 1 predicted drop out at time 2 (OR = 1.29, 95% CI = 1.19 - 1.39, p<.001), also a 1 SD increase in oppositionality at time 2 predicted drop out at time 3 (OR = 1.22, 95% CI = 1.09 – 1.40, p <.001). The OR for a 1 SD increase in depressed mood at time 1 did not predict drop out at time 2 (OR = 1.04, 95% CI = .96 – 1.13, p = .31), also a 1 SD increase in depressed mood at time 2 did not predict drop out at time 3 (OR =1.09, 95% CI = .97 – 1.22, p = .12) (see Appendix C).

2.3.2 Measures

Antisocial behaviour. Antisocial behaviour was assessed using 15 items from the Youth Self Report (YSR) (Achenbach, 1991) and Adult Self Report (ASR) (Achenbach & Rescorla, 2003) which address the previous 6 months and are based on a 3-point scale (0 = not true, 1 = somewhat true, 2 = very true). The items used to measure antisocial behaviour are not fully consistent across time points to ensure they are developmentally appropriate. For this study, 15 items were chosen that were conceptually equivalent at each time point. Example items include ‘Stealing’ and ‘Getting into many fights’ (see Appendix B). In previous studies using G1219 dataset (Rowe et al., 2006; Rowe et al., 2008) antisocial behaviour was measured from the externalising items subtyped into oppositionality, delinquency and physical aggression, only delinquency and oppositionality were independently associated with depressed mood. The same subtyping was adopted for the current thesis, however, due to lack of independent association between physical aggression and depressed mood in a previous study (Rowe et al., 2006), this was not included in the current study. The behaviours covered map onto the DSM-5 behaviours including ODD and CD. The scale for delinquency has a range of 0-15, the scale for oppositionality range from 0-15, higher scores on each subscale indicate higher antisocial behaviour. In the present sample, the subscale showed acceptable internal reliability (oppositionality αs = .67, .71, .74 at time 1, 2 and 3 respectively; delinquency αs = .60, .62, .59 at time 1, 2 and 3 respectively).

Depressed mood. The short version of the Mood and Feeling Questionnaire (SMFQ) (Angold et al., 1995) measured depressed mood at all-time points. This measure comprises 13 items addressing major depression symptoms experienced during the past 2 weeks. Example items include 'I thought I could never be as good as others' and 'I cried a lot' (see Appendix A). As one of the initial aims of the G1219 study was molecular genetics analysis of extreme scoring group, a 4-point response format (0 = never, 1 = sometimes, 2 = often, 3 = always) was used at time 1 to allow better discrimination of the lower end of the spectrum. The standard 3-point scale (0 = not true, 1 = sometimes, 2 = true) was used at time 2 and 3. The 13 items were summed with higher scores indicating greater depression. The scale has a range of 0-39, with higher scores indicating higher depression. This measure showed good internal consistency in the present sample (αs = .90, .88, .90 at time 1, 2 and 3 respectively).

2.3.3 Statistical analyses

Descriptive statistics were conducted using Stata (StataCorp, 2007). Mplus version 7.3 was used for latent variable modelling (Muthén & Muthén, 1998-2012). The non-independence of within-family observations was taken into account using ‘Type = Complex’ command to adjust the standard errors for clustered sampling. The Weight Least Square Estimator (WLSE) with means adjusted and variance adjusted chi-square test statistics was used to estimate parameters because categorical items were used. Missing data were handled using listwise deletion.

2.3.3.1 Exploratory Factor Analysis

Exploratory Factor Analyses (EFA) was first used to examine the underlying structure of chosen antisocial items on half of the data at times 1, 2, and 3, with the items treated as ordinal rather than assumed to be continuous. EFA was conducted to test whether the usual subtyping of antisocial behaviour constructs provided psychometrically valid constructs in this dataset across time. The nature and number of latent variables underlying the item set was determined by examining eigenvalues and scree plot; a ‘Geomin’ (oblique) rotation was used because it was expected that extracted factors would be correlated. In order to check how robust the resultant measurement model was, it was tested via a Confirmatory Factor Analysis (CFA) using the other half of the dataset.

2.3.3.2 Confirmatory Factor Analysis

CFA was then performed on the antisocial behaviour and depressed mood items, using the full dataset. For the antisocial behaviour items, we employed the measurement model that had emerged from the previous stage of analysis, with the depressed mood items loading on to a single factor. Tests of longitudinal and between group measurement invariance were carried out to examine whether the psychometric properties of the observed indicators were generalisable across time and sex.

2.3.3.3 Measurement invariance

Testing for measurement invariance be it across time or between groups involved the following stages: first a configural invariance model with no equality constrains on parameters was tested to determine whether simply maintaining the same configuration of items and factors across time/between groups resulted in a satisfactory fit. Next a metric invariance model fixed factor loadings equal across time/between groups. The strong invariance model also fixed thresholds equal; the final strict invariance model also constrained item residual variance to be equal. In all models, autocorrelations were fitted between identical items measured at adjacent time points.

2.3.3.4 Structural equation models

The measurement model was then extended to a structural equation model (SEM) with autoregressive paths modelling stability within traits and cross-lagged paths modelling cross-trait associations across time. Given there were three-time points of data, the pattern of effects between time 1 and time 2 were replicated between time 2 and time 3. Initially, a 'Full' model, containing all the hypothesised pathways from all the variables, with all introduced paths free to be estimated was fitted (Model 1, see Figure 2.1) followed by a series of competing constrained models. Models 2a to 2d constrained autoregressive paths within traits to be equal separately for each trait (2a-2c), and then for all traits (2d), thus testing the stability of these relationships over time. Models 3a to 3i constrained between traits by fixing individual cross-lagged paths equal in turn (Models 3a-3f) and then pairs/combinations of paths (3g-3i). The fits of these models were compared against the preceding best model. The final set of models, 4a to 4d constrained pairs, then all cross-direction effects to be equal against the best preceding model.

Throughout these analyses, we report the differences in chi-square, but given that standard model comparison via a chi-square difference test would be affected by the large sample (i.e. even trivial improvements in model fit will yield a statistically significant improvement), we only took significant differences to be meaningful when CFI criterion was also met by following the advice of Cheung and Rensvold (2002) in using a fit index based model comparison protocol.

The following indices of fit in SEM were used in the current study:

2.3.3.4.1 Comparative Fit Index (CFI)

The CFI takes account of sample size and performs well even when sample size is small. Values for CFI range between .0 and 1.0 with values closer to 1.0 indicating good fit. A cut-off criterion of CFI ≥.95 is recognised as indicative of good fit (Hu & Bentler, 1999). Computation of the CFI is as follows:

$$CFI = 1 - [(\chi^2_H - df_H) / (\chi^2_B - df_B)]$$

$\chi^2_H = \chi^2$ value of the hypothesised model

$df_H = df$ of the hypothesised model

χ^2_B = χ^2 value of the baseline model

df_B = df of the baseline mode

2.3.3.4.2 Tucker-Lewis Index (TLI)

TLI is based on the comparison of the implied matrix with that of the null model. A value of 1 indicates perfect fit. A cut-off value ≥.95 is considered as good fit. Computation of TLI is as follows:

$$TLI = [(\chi^2_B / df_B) / (\chi^2_H / df_H)] - (\chi^2_B / df_B) - 1]$$

2.3.3.4.3 Root Mean Square Error of Approximation (RMSEA)

RMSEA is used to inform about how well the model would fit the population. A value of 0 indicates perfect fit. A cut-off value ≤.06 is considered as good fit (Hu & Bentler, 1999). The RMSEA is expressed per degree of freedom, which results in sensitivity to the number of estimated parameters in the model. The RMSEA computation is carried out in two steps. In the first step, the index approximates a noncentral χ^2 distribution. This distribution has an additional parameter referred to as the noncentrality parameter (δ). This tests whether the null hypothesis is false. The δ_H value is rescaled as follows:

$$\delta_H = (\chi^2_H / df_H) / N$$

From the above δ_H formula, the resulting computation of the RMSEA is as follows:

$$RMSEA = \sqrt{} (\delta_H / df)$$

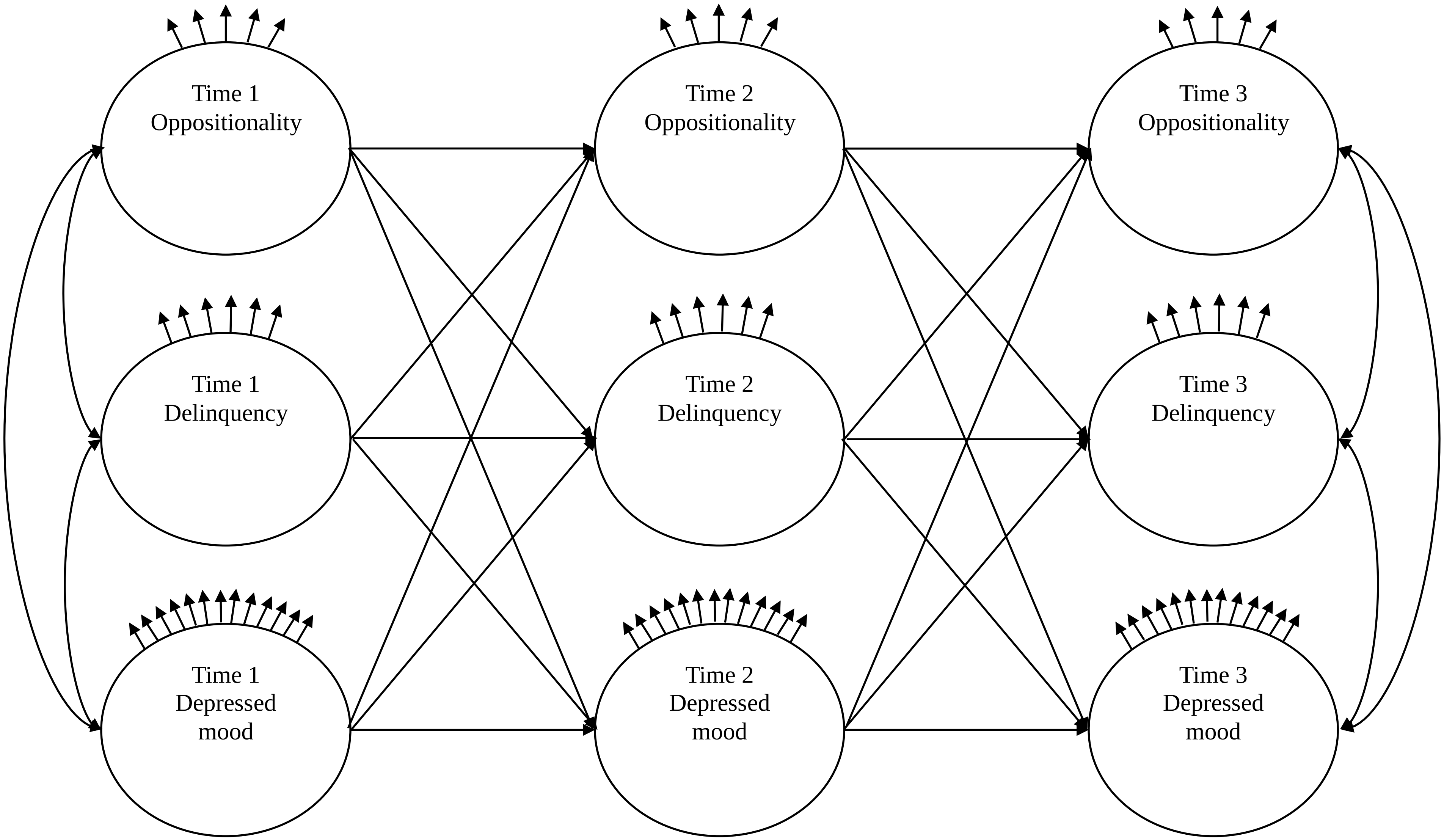

Figure 2.1 Autoregressive cross-lagged model of the association between oppositionality, delinquency and depressed mood at three time points

Note: Autoregressive paths = pathways within constructs over time (e.g. Oppositionality at Time 1 to Oppositionality at Time 2); Cross lagged paths = pathways between constructs over time (e.g. Oppositionality at Time 1 to Depressed mood at Time 2). Arrows above each factor represent the observed items that load onto them but cannot be pictured due to space constraints.

2.4 Results

2.4.1 Factor analysis

An EFA was conducted on a randomly selected half of the sample to establish a measurement model for the antisocial behaviour items at each of the three time points. At each time point, a two-factor solution was supported by examination of the scree plot and the factor loadings (see Table 2.1).

Factor loadings greater than .40 were retained for further analyses. However, Item_3 (Disobedient) which had a factor loading above the threshold (>.40) across the three time points was removed from further analyses as this was not conceptually part of delinquency. The two factors were consistent and interpretable in terms of oppositionality (5 items) and delinquency (6 items). The adequacy of the two-factor model for antisocial behaviour at three time points was verified with a CFA performed on the other half of the sample (CFI = .92, TLI = .92, RMSEA = .03).

Table 2.1 Factor loadings of dependent variables in a two-factor solution

Variable	Time 1		Time 2		Time 3	
	OPP	DEL	OPP	DEL	OPP	DEL
Item_1: argues a lot	**.743**	-.013	**.873**	-.164	**.805**	-.056
Item_2: mean to others	**.526**	.198	**.430**	.230	**.480**	.290
Item_3: disobedient	.056	.774	.031	.858	.001	.833
Item_4: screams a lot	**.589**	-.066	**.709**	.023	**.823**	.002
Item_5: has a hot temper	**.713**	.032	**.718**	.002	**.783**	.001
Item_6: stubborn	**.531**	.019	**.573**	.059	**.628**	.038
Item_1: lacks guilt	-.074	**.461**	.067	**.481**	-.006	**.563**
Item_2: deviant peers	.011	**.711**	-.062	**.741**	.005	**.651**
Item_3: lies	.157	**.505**	.195	**.516**	.138	**.620**
Item_4: steals	.001	**.617**	.009	**.801**	-.018	**.704**
Item_5: truancy	-.009	**.693**	-.038	**.686**	.033	**.607**
Item_6: use alcohol	-.100	**.581**	-.035	**.583**	-.089	**.526**

Note: Factor loadings >.40 consistently across the three time points are in bold. OPP = oppositionality, DEL = delinquency.

2.4.2 Descriptive statistics and zero-order correlations

Descriptive statistics are and zero-order correlations for depressed mood and antisocial subscales are presented in Table 2.2. There were continuities in depressed mood and antisocial behaviour subscales across time. The cross-trait correlations were also significant between all traits across time.

Table 2.2 Mean scores (standard deviations) and zero-order correlations (with 95% confidence intervals) between the observed variables at three time points

	Variable	N	Mean (SD)	1	2	3	4	5	6	7	8	9
1	Time 1 Depressed mood	2636	8.05 (6.64)	–								
2	Time 1 Delinquency	2628	1.65 (1.75)	.29 (.25-.32)	–							
3	Time 1 Oppositionality	2628	2.76 (1.99)	.42 (.38-.45)	.38 (.35-.41)	–						
4	Time 2 Depressed mood	1592	6.24 (5.33)	.47 (.43-.50)	.16 (.12-.21)	.29 (.24-.33)	–					
5	Time 2 Delinquency	1592	1.43 (1.71)	.17 (.12-.22)	.46 (.42-.50)	.25 (.20-.29)	.25 (.21-.30)	–				
6	Time 2 Oppositionality	1595	2.25 (1.97)	.27 (.22-.31)	.28 (.24-.33)	.53 (.50-.57)	.41 (.37-.45)	.41 (.37-.45)	–			
7	Time 3 Depressed mood	1550	6.45 (5.73)	.38 (.34-.42)	.13 (.08-.18)	.21 (.16-.26)	.47 (.43-.51)	.12 (.06-.17)	.25 (.19-.30)	–		
8	Time 3 Delinquency	1552	1.45 (1.54)	.10 (.05-.15)	.32 (.28-.37)	.14 (.09-.19)	.16 (.10-.21)	.42 (.38-.47)	.28 (.22-.33)	.21 (.16-.26)	–	
9	Time 3 Oppositionality	1552	1.98 (1.93)	.18 (.14-.23)	.22 (.17-.26)	.38 (.34-.42)	.25 (.19-.30)	.22 (.17-.27)	.52 (.47-.55)	.40 (.36-.44)	.33 (.29-.37)	–

Note: N = number of participants. All correlations were significant at the $p<.01$ level (two-tailed).

2.4.3 Measurement invariance

Tests of measurement invariance over time are presented in Table 2.3, this includes both antisocial behaviour and depressed mood items. A model specifying configural invariance indicated an adequate fit to the data, supporting there being the same number of factors at each time point with the same pattern of fixed and free parameters. The next step tested whether there were differences in the factor loadings (items) across time by constraining them to be equal at times 1, 2 and 3. This constrained model, specifying metric invariance, did not lead to a significant loss of fit according to CFI. This suggested the factor loadings were invariant and that the factor loadings for all the constructs (delinquency, oppositionality, and depressed mood) have the same meaning across the three time points. However, the strong and strict invariance models led to substantial decrease in CFI which indicated that the thresholds differed across time point; therefore, the metric invariance model was selected as best fitting overall model.

Next we tested factorial invariance across sex. The configural model provided an adequate fit to the data; this was extended to a metric invariance model by constraining factor loadings across groups which provided similar fit to the configural model. However, further constraining to strong and strict invariance provided a worse fit so the metric invariance model was preferred.

Table 2.3 Model fit and comparisons for measurement invariance across time and sex

	Model	N	χ^2	*df*	P	$\Delta\chi^2$	Δdf	P	CFI	TLI	RMSEA
Time	Configural	2641	4456.86	2376	.00	-	-	-	.969	.967	.018
	Metric	**2641**	**4504.93**	**2418**	**.00**	**146.39**	**42**	**.00**	**.969**	**.967**	**.018**
	Strong	2641	7593.93	2515	.00	5542.32	92	.00	.924	.923	.028
	Strict	2641	7639.71	2563	.00	96.82	48	.00	.924	.925	.027
Sex	Configural	2638	6689.61	4945	.00	-	-	-	.970	.969	.016
	Metric	**2638**	**6686.96**	**4966**	**.00**	**41.50**	**21**	**.01**	**.971**	**.970**	**.016**
	Strong	2638	7989.44	5113	.00	2133.26	147	.00	.951	.951	.021
	Strict	2638	7971.47	5137	.00	616.40	33	.00	.952	.952	.020

Note: N = number of participants; χ^2 = chi-square; *df* = degrees of freedom, $\Delta\chi^2$ = change in chi-square; Δdf = change in degrees of freedom; P = probability; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation. Configural = no equality constraint; Metric = equality constraint on common factor loadings; Strong = equality constraint on loadings and thresholds; Strict = equality constraint for variances. The best models from the measurement invariance across time and sex are in bold.

2.4.4 Autoregressive cross-lagged model

The best fitting measurement model (metric invariance across time and sex) was extended to specify autoregressive cross-lagged paths across time (see Table 2.4). The baseline model included all paths without constraints (Model 1) produced good model fit (CFI = .971, TLI = .970, RMSEA = .016). In Model 2, autoregressive paths were fixed equal across time for each trait separately (Model 2a = delinquency; 2b = oppositionality; 2c = depressed mood) whilst allowing cross-lagged paths to be freely estimated. The model fit improved by constraining all of the autoregressive to be equal across time (Model 2d: CFI = .971, TLI = .971, RMSEA = .016).

The next step constrained cross-lagged pathways to be equal across traits separately (Model 3) which contributed to a significant improvement in the model fit (Model 3i: CFI = .972, TLI = .971, RMSEA = .016). The final model (Model 4) involved constraining all cross-lagged pathways across traits to be equal, this was significantly improved by adding constraint to all cross-lagged across direction pathways (Model 4d: CFI = .972, TLI = .971, RMSEA = .016). The final model included significant pathways from depressed mood to oppositionality between time 1 to 2, and between time 2 to 3 (see Figure 2.2). However, other cross-lagged pathways were not statistically significant.

Table 2.4 Autoregressive cross-lagged model tests

Model		χ^2	*df*	P	$\Delta\chi^2$	Δ*df*	P	CFI	TLI	RMSEA (90% CI)
1. 'Full': Autoregressive cross-lagged		6688.64	4978	.00	–	–	–	.971	.970	.016 (.015 - .017)
2. Autoregressive pathways	a) DEL (fixed) vs 1	6694.34	4981	.00	8.81	3	.03	.971	.970	.016 (.015 - .017)
	b) OPP (fixed) vs 1	6688.24	4981	.00	2.49	3	.48	.971	.970	.016 (.015 - .017)
	c) DEP (fixed) vs 1	6673.23	4981	.00	4.27	3	.23	.971	.971	.016 (.015 - .017)
	d) All (fixed)	**6679.06**	**4987**	**.00**	–	–	–	**.971**	**.971**	**.016 (.015 - .017)**
	All, test vs 2a	6679.06	4987	.00	7.47	6	.28	.971	.971	.016 (.015 - .017)
	All, test vs 2b	6679.06	4987	.00	9.22	6	.16	.971	.971	.016 (.015 - .017)
	All, test vs 2c	6679.06	4987	.00	10.26	6	.11	.971	.971	.016 (.015 - .017)
3. Cross-lagged	a) DEL on DEP (fixed) vs 2d	6665.98	4990	.00	3.64	3	.30	.972	.971	.016 (.015 - .017)
- across traits	b) OPP on DEP (fixed) vs 2d	6669.76	4990	.00	4.45	3	.22	.972	.971	.016 (.015 - .017)
	c) DEP on DEL (fixed) vs 2d	6672.59	4990	.00	1.25	3	.74	.972	.971	.016 (.015 - .017)
	d) DEP on OPP (fixed) vs 2d	6669.40	4990	.00	.29	3	.96	.972	.971	.016 (.015 - .017)
	e) OPP on DEL (fixed) vs 2d	6676.48	4990	.00	1.55	3	.67	.972	.971	.016 (.015 - .017)
	f) DEL on OPP (fixed) vs 2d	6685.69	4990	.00	8.34	3	.04	.972	.971	.016 (.015 - .017)

	g) DEP on OPP and DEL (fixed) vs 2d	6663.44	4993	.00	1.60	6	.95	.972	.971	.016 (.015 - .017)
	h) DEL and OPP on DEP (fixed) vs 2d	6687.51	4993	.00	18.55	6	.01	.972	.971	.016 (.015 - .017)
	i) All (fixed)	**6662.40**	**5005**	**.00**	–	–	–	**.972**	**.971**	**.016 (.015 - .017)**
	All, test vs 3a	6662.40	5005	.00	31.37	15	.01	.972	.971	.016 (.015 - .017)
	All, test vs 3b	6662.40	5005	.00	30.54	15	.01	.972	.971	.016 (.015 - .017)
	All, test vs 3c	6662.40	5005	.00	31.58	15	.01	.972	.971	.016 (.015 - .017)
	All, test vs 3d	6662.40	5005	.00	32.45	15	.01	.972	.971	.016 (.015 - .017)
	All, test vs 3e	6662.40	5005	.00	30.92	15	.01	.972	.971	.016 (.015 - .017)
	All, test vs 3f	6662.40	5005	.00	28.93	15	.02	.972	.971	.016 (.015 - .017)
	All, test vs 3g	6662.40	5005	.00	28.73	12	.00	.972	.971	.016 (.015 - .017)
	All, test vs 3h	6662.40	5005	.00	9.43	12	.67	.972	.971	.016 (.015 - .017)
4. Cross-lagged	a) DEP and DEL (fixed) vs 3i	6656.75	5006	.00	.52	1	.47	.972	.971	.016 (.015 - .017)
- across direction	b) DEP and OPP (fixed) vs 3i	6668.52	5006	.00	3.50	1	.06	.972	.971	.016 (.015 - .017)
	c) OPP and DEL (fixed) vs 3i	6662.41	5006	.00	1.51	1	.22	.972	.971	.016 (.015 - .017)
	d) All (fixed)	**6682.42**	**5008**	**.00**	–	–	–	**.972**	**.971**	**.016 (.015 - .017)**
	All, test vs 4a	6682.42	5008	.00	14.63	2	.00	.972	.971	.016 (.015 - .017)

All, test vs 4b	6682.42	5008	.00	11.62	2	.00	.972	.971	.016 (.015 - .017)
All, test vs 4c	6682.42	5008	.00	11.90	2	.00	.972	.971	.016 (.015 - .017)

Note: N= 2532; χ^2 = chi-square; *df* = degrees of freedom, $\Delta\chi^2$ = change in chi-square; Δ*df* = change in degrees of freedom; P = probability; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval. DEP = Depressed mood; DEL = Delinquency; OPP = Oppositionality. The best model at each stage which are taken forward are in bold.

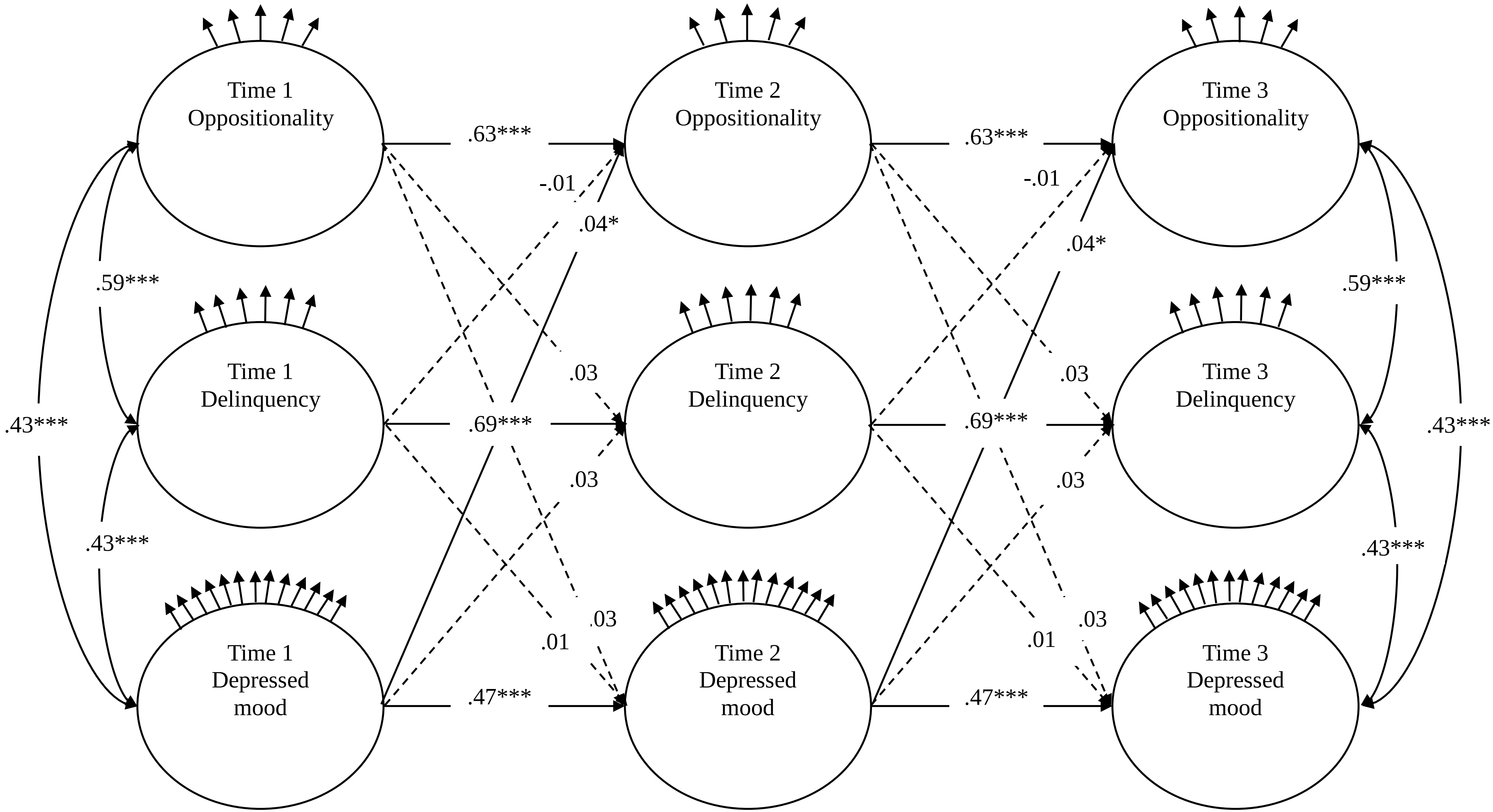

Figure 2.2 Standardised autoregressive cross-lagged model of antisocial behaviour subscales and depressed mood across three time points.

Note: Dotted lines represent nonsignificant results. *p<.05 level; ** p<.01; ***p<.00. Arrows above each factor represent the observed items that load onto them but cannot be pictured due to space constraints.

2.5 Discussion

Using an autoregressive cross-lagged model over three time points, this study examined longitudinal associations between delinquency and oppositionality with depressed mood from adolescence to young adulthood. The aim of this study was to examine three models: failure, acting out and mutual reinforcement model. In order to do this, we assessed the direction of the pathways between antisocial behaviour and depressed mood across three time points taking into account the heterogeneity of antisocial behaviour. Previous studies have found antisocial behaviour is not a unitary construct (Rowe et al., 2006; Rowe et al., 2008; Tackett et al., 2003). Our factor analysis results confirmed a two-factor structure with oppositionality and delinquency. Some of the previous studies utilised clinical populations, and some population studies. The current study extends a previous study using a single wave of G1219 data (Rowe et al., 2006) to a longitudinal analysis across three time points.

2.5.1 Autoregressive paths

The autoregressive paths modelled continuities across time points for all traits. Delinquency and oppositionality subtypes of antisocial behaviour showed significant continuities across time in line with previous studies (Brennan, Hall, Bor, Najman, & Williams, 2003; Loeber, 1982). Similarly, depressed mood showed continuity across time in line with previous studies (Fombonne et al., 2001).

2.5.2 Cross-lagged paths

Paths from depressed mood at an earlier time to oppositionality at the later time were significant but not vice versa. Other pathways from depressed mood and delinquency were not significant. The findings are most consistent with the acting out model (Carlson & Cantwell, 1980; Kofler et al., 2011; Wiesner, 2003). In line with this model, depressed mood led to oppositionality at different time points. However, the current results did not support the failure model, previous work suggested that the path from delinquency to depressed mood may operate via life events experienced by individuals. For example, negative life event (Rowe et al., 2006; Timmermans, van Lier, & Koot, 2010) and negative experiences (Wertz et al., 2015) has been found to be involved as mediators from delinquency to depressed mood. There are a number of possible explanations for the longitudinal links between depressed mood and antisocial behaviour. One possibility is that the same genes may influence both phenotypes. Both are highly heritable (Rhee & Waldman, 2002; Rice et al., 2002) and genetic effects account for a substantial proportion of the overlap between the two traits (O'Connor, McGuire, et al., 1998; O'Connor, Neiderhiser, et al., 1998; Rowe et al., 2008).

The association between antisocial behaviour and depression may differ across development as shown in a previous study associations were identified in young children aged between 7 and 10 years (Wertz et al., 2015). A clinical population study has also shown an association between conduct problem and later depression in preadolescents (Capaldi & Stoolmiller, 1999).

2.5.3 Limitations

This study provides the advantage of having a large community sample measured over repeated time points. Structural equation modelling is a powerful multivariate analysis which allows for confirmatory and explorative modelling for theory testing and theory development. This method also enables for the ability to construct latent variables. On the other hand, the results should be interpreted in the context of a number of limitations. First, all measures were self-reported, raising the possibility that associations may have been inflated due to shared method variance. However, this method of assessment can also be considered a strength as individuals can report on aspects of their own behaviour which may not be known to others. Replication with multi-informants (e.g. parent, siblings and teacher) would be of value. Second, the self-report measures were based on different sampling frames, for example, depressed mood was based on the past two weeks whereas antisocial behaviour scales were based on the last six months. However, previous studies have used similar sampling time frame for antisocial behaviour and depressed mood (Rowe et al., 2006; Rowe et al., 2008). Replicating using different reports with similar time-frame would be beneficial.

2.5.4 Conclusion

The findings reported in this chapter supports the acting out model with a developmental perspective. It also supports the cross-sectional association between antisocial behaviour and depressed mood. Given that this does not appear to be substantially driven by cross-lagged effects, it is likely to emerge early in development and may be due to shared risk factors that are present from early in development. Genetic effects fit this definition and their role in comorbidity will be investigated in the next chapter by utilising twin analyses to identify the basis for the strong cross-sectional association identified in this study.

Chapter 3 A twin and sibling study of antisocial behaviour and depressed mood: Associations from adolescence to adulthood

3.1 Overview

This chapter investigates the aetiology of the association between antisocial behaviour and depressed mood using longitudinal behavioural genetic analysis. A multivariate Cholesky decomposition was used to examine genetic and environmental effects on antisocial behaviour and depressed mood over three time points. Moderate phenotypic associations were found between antisocial behaviour and depressed mood. Significant genetic and nonshared environmental effects were identified on both traits but shared environmental effects were not significant. Genetic effects were found at the first time point. These continued to influence later time points and there was evidence of further genetic effects becoming influential later in development for antisocial behaviour and depressed mood. In contrast, nonshared environmental influences were specific to each time point. There was no evidence that genetic effects specific to one form of psychopathology at an earlier time point were influential in the other form of psychopathology at later time point.

3.2 Introduction

In the previous chapter, strong within-trait stability in both antisocial behaviour subtypes (oppositionality and delinquency) and depressed mood was found over time. Also, strong cross-trait correlations at each time point were found but no interplay over time. This chapter will investigate the basis for this association. There are multiple explanations for comorbidity (Angold et al., 1999; Caron & Rutter, 1991). For example, overlap between traits can reflect measurement issues such as overlap of diagnostic criteria. Alternatively, the overlap may reflect one trait leading to another (Caron & Rutter, 1991). Shared genetic and/or environmental risk factors may also contribute to the overlap of antisocial behaviour and depressed mood.

One way for understanding the nature of etiological overlap between antisocial behaviour and depressed mood is through the use of genetically informative samples. Each trait is moderately heritable with estimates typically ranging between 30-50% for depression (Rice et al., 2002) and around 50% for antisocial behaviour (Rhee & Waldman, 2002; Sullivan, Neale, & Kendler, 2000). The few available twin studies suggest that a substantial proportion of the overlap between antisocial behaviour and depressed mood can be accounted for by genetic effects. Shared genetic effects have been found to account for 45% of covariation between antisocial behaviour and depression, with 30% attributable to shared environmental effects and 25% to nonshared environment effects (O'Connor, Neiderhiser, et al., 1998). Cross-sectional analyses of the G1219 dataset have previously found that 56% to 60% of the association between subscales of antisocial behaviour (delinquency, oppositionality and physical aggression) and depressed mood was attributable to overlapping genetic effects with the remainder attributable to nonshared environmental effects (Rowe et al., 2008).

Finding overlapping genetic effects is consistent with the genetic pleiotropy hypothesis in that the overlap between antisocial behaviour and depressed mood may be explained by generalist genes, which are influential across a range of emotional and behavioural problems (Eley, 1997). Conversely, environmental effects appear to influence individual traits specifically. Therefore, environmental effects may account for the differences between behaviour problems.

Behavioural genetic studies exploring the association between antisocial behaviour and depression in childhood and adolescence have largely focussed on concurrent associations and so do not provide information about change over time. However, Wertz et al. (2015) followed participants from childhood to preadolescence (age 5 to 12 years) examining the role of negative experiences (bullying victimisation, academic difficulties and maternal dissatisfaction) in the association between early externalising problems (e.g. aggression, rule-breaking, oppositional behaviour) and later internalising symptoms (e.g. depression and anxiety). Negative experiences partially mediated this association in phenotypic analyses. Behavioural genetic analyses showed that genetic effects specific to age 5 externalising problems also influenced internalising problems at age 12. Thus, genetic influences from early externalising problems were associated with later internalising problems.

3.2.1 Aims

In this study we examine longitudinal associations between antisocial behaviour and depressed mood from adolescence to early adulthood (mean ages 15, 17 and 20 years) in a genetically informative design. In the previous chapter, delinquency and oppositionality showed significant association with depressed mood, therefore in this chapter both subscales will be combined to represent antisocial behaviour scale. In addition, physical aggression will be combined with delinquency and oppositionality to increase the coverage of the scale to include the full spectrum of CD and ODD symptomatology. We test whether the finding from Wertz et al. (2015) that genes influencing externalising problems also affect later internalising problems is also evident at this later developmental period.

3.3 Method

3.3.1 Sample

The sample consisted of twins and siblings from the G1219 longitudinal study, from waves 2, 3 and 4 as outline in Chapter 2 (section 2.3.1).

3.3.2 Measures

Antisocial behaviour. Antisocial behaviour was assessed using 15 items from the Youth Self Report (YSR) (Achenbach, 1991) and Adult Self Report (ASR) (Achenbach & Rescorla, 2003) which address the previous 6 months and are based on a 3-point scale (0 = not true, 1 = somewhat true, 2 = very true). The items used to measure antisocial behaviour are not fully consistent across time points to ensure they are developmentally appropriate. The 15 items were chosen to be conceptually equivalent at each time point. Six items represent delinquency, five items represent oppositionality and three items represent physical aggression sub-scales. These items were summed together to create a combined antisocial behaviour scale containing 14 items. Example items include 'Stealing' and 'Getting into many fights'. In the present sample, the antisocial behaviour scale showed good reliability (αs = .80, .80, .78 at time 1, 2 and 3 respectively).

Depressed mood. The short version of the Mood and Feeling Questionnaire (SMFQ) (Angold et al., 1995) measured depressed mood at all-time points. This measure comprises 13 items addressing major depression symptoms experienced during the past 2 weeks. Example items include 'I thought I could never be as good as others' and 'I cried a lot'. A 4-point response format (0 = never, 1 = sometimes, 2 = often, 3 = always) was used at time 1 and the standard 3-point scale (0 = not true, 1 = sometimes, 2 = true) was used at time 2 and 3. The 13 items were summed to give a total depression score with higher scores indicating greater depression. SMFQ scores show a unifactorial structure reflecting the core construct of depression. This measure shows good internal consistency in the present sample (αs = .90, .88, .90 at time 1, 2 and 3 respectively).

3.3.3 Statistical analyses

Phenotypic analyses were conducted using Stata (StataCorp, 2007) which adjusts the standard errors and associated p-values for clustering of twins and sibling responses by treating the family as the primary sampling unit. Skewness was high for depressed mood at time 1 (skew = 1.35, SE=.05), time 2 (skew = 1.14, SE = .06) and time 3 (skew = 1.26, SE = .06); also high for antisocial behaviour at time 1 (skew = 1.31, SE =.05), time 2 (skew = 1.51, SE = .06) and time 3 (1.72; SE=.06), so they were square-root transformed. Skewness was acceptable after transformation for depressed mood at time 1 (skew = .51, S.E = .05), time 2 (skew = .41, S.E = .06) and time 3 (skew = .50, S.E = .06) and for antisocial behaviour at time 1 (skew = .46, S.E = .05), time 2 (skew = .60, S.E = .06) and time 3 (skew = .69, S.E = .06). All analyses (excluding descriptive statistics) focus on square-root transformed variables.

Genetic models were fitted using OpenMx (Boker et al., 2011) in R, a structural equation modelling package for the analysis of genetically informative data. Twin designs compare the relative similarity of MZ twins who are genetically identical, with the similarity of DZ twins and non-twin siblings who share 50% of their genes on average. Estimation of the influence of additive genetic (A), shared environment (C; environmental factors that make siblings alike) and nonshared environment (E; environmental factors which make siblings different from one another, plus measurement error) can be achieved by comparing the within pair correlation of MZ twins with DZ twins and siblings. All variables were age and sex regressed as is standard in twin modelling (McGue & Bouchard, 1984).

3.3.3.1 Univariate analyses

Univariate analyses assessing the influence of A, C and E were conducted on antisocial behaviour and depressed mood at all three time points. Univariate analyses estimate the cross twin/sibling same-trait correlations in pairs of MZ twins and DZ twins and non-twin siblings separately. In the univariate analyses the genetic and environmental influences on each trait was estimated using the difference in similarity between these groups. Univariate models estimate the contribution of A, C and E (see Figure 3.1).

Similarity between MZ twins for a specific trait is accounted for by genetics and shared environment, both A and C equal 1 since MZ twins share 100% of their genetic make-up and their shared environment:

$$rMZ = A + C$$

However, DZ twins only share 50% of their segregating genes, thus the similarity in these twins for A is half:

$$rDZ = \frac{1}{2} A + C$$

The twin correlation can be used to calculate the proportion of genetic and environmental influence on a particular trait. The additive influence is calculated as twice the difference in the MZ and DZ twin correlation:

$$A = 2(rMZ - rDZ)$$

The proportion of the shared environment influence can be calculated as the difference between the MZ correlation and additive genetics:

$$C = r\text{MZ} - A$$

The proportion of nonshared environmental influence can be calculated as the total variance in a trait minus the MZ correlation:

$$E = 1 - r\text{MZ}$$

Path diagrams are used to describe genetic analyses in a visual way which can be used to calculate the different proportion of variance from A, C and E.

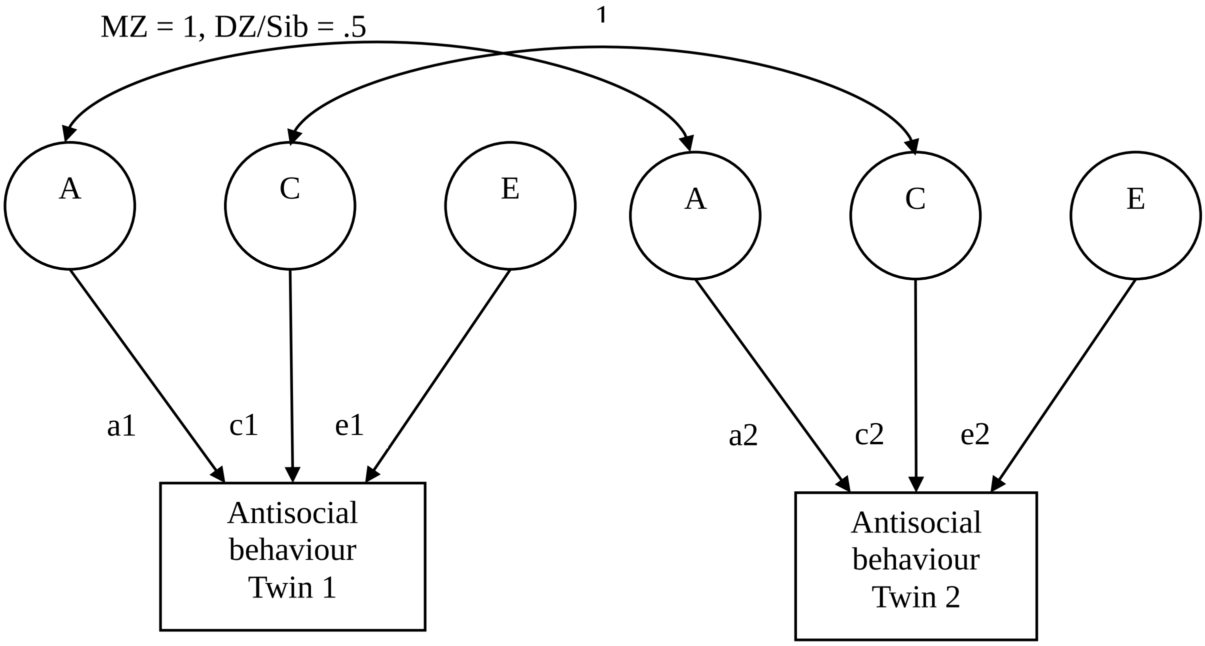

Figure 3.1 Path diagram for a univariate ACE model for one twin pair.

Note: MZ = monozygotic; DZ = dizygotic; Sib = siblings; A = additive influence; C = shared environmental influence; E = nonshared influence; a1, c1, e1 = etiological influences on twin 1; a2, c2, e2 = etiological influences on twin 2.

3.3.3.2 Multivariate Cholesky decomposition

The univariate genetic model was extended to a multivariate level to answer the question regarding multiple phenotypes simultaneously over time using a longitudinal Cholesky decomposition model. Multivariate models also examine the within-twin and the cross-trait covariance's between pairs of MZ and DZ twins and non-twin siblings separately in order to investigate the aetiological factors influencing the relationships between traits. If MZ twin associations are greater than DZ or sibling pairs this implies additive genetic influences. If the association between MZ pairs is similar to DZ or sibling pairs this implies environmental influences. Nonshared environmental influence is implied when there is no significant cross-twin or sibling cross-trait correlations.

Cholesky decomposition is the most common multivariate technique used in the classical twin design. Cholesky decomposition in this study assumes six distinct sets of genetic and environmental factors (A_1 to A_6, C_1 to C_6, and E_1 to E_6). In this model A_1 includes all genetic variance common to depressed mood and antisocial behaviour across all three time points. A_2 identifies residual genetic effects that explain variance in antisocial behaviour at time 1 and both traits at time 2 and 3. A_3 represents genetic influences common to all traits at time 2 and beyond but not involved in either trait at time 1; A_4 represents genetic influences on antisocial behaviour but not depressed mood at time 2 and both depressed mood and antisocial behaviour at time 3. A_5 represents genetic influences on all traits at time 3 but not at time 1 or 2. A_6 represents genetic influences only for antisocial behaviour at time 3 that are not shared with any other traits in the model. The same principles apply to shared environment (C) and nonshared environment (E) variance for both models.

The order of variables: time 1 depressed mood, time 1 antisocial behaviour, time 2 depressed mood, time 2 antisocial behaviour, time 3 depressed mood, and time 3 antisocial behaviour (see Figures 3.2, 3.3, 3.4). Another possible configuration is to order variables so that antisocial behaviour precedes depressed mood at each time point (antisocial behaviour time 1, depressed mood time 1, antisocial behaviour time 2, depressed mood time 2, antisocial behaviour time 3, depressed mood time 3). This configuration provides an identical model fit but illustrates different aspect of the overlaps between sources of variance contributing to antisocial behaviour and depressed mood. We provide parameter estimates, but not fit statistics from this approach (see Figure 3.6).

Prior to fitting biometric genetic models, saturated models were fitted to the data. Saturated models estimate the maximum number of parameters to describe variances, covariance, and means of traits and can be used to obtain a baseline index of fit. A nested model was fitted by dropping certain parameters from the model and this was compared to the full models. Parameters which result in non-significant change in model fit can be dropped from the model which will eventually reach the most parsimonious model. Best fitting models were selected using two fit indices: twice the negative log likelihood (-2LL) of the data and the Akaike Information Criterion (AIC). The difference in the log likelihoods of nested models can be tested using the chi-square (χ^2) test. A non-significant χ^2 difference and low AIC values indicate a well-fitting model (Neale & Cardon, 1992).

3.4 Results

3.4.1 Descriptive statistics

Descriptive statistics are presented in Table 3.1. Males scored higher than females on antisocial behaviour at time 1 ($t(2263) = 3.96$, $p<.001$), time 2 ($t(1586) = 3.85$, $p<.001$), and time 3 ($t(1036) = 4.38$, $p<.001$), and females scored higher on depressed mood at time 1

($t(2624) = -9.90$, $p<.001$), time 2 ($t(1478) = -7.71$, $p<.001$), and time 3 ($t(1366) = -4.89$, $p<.001$).

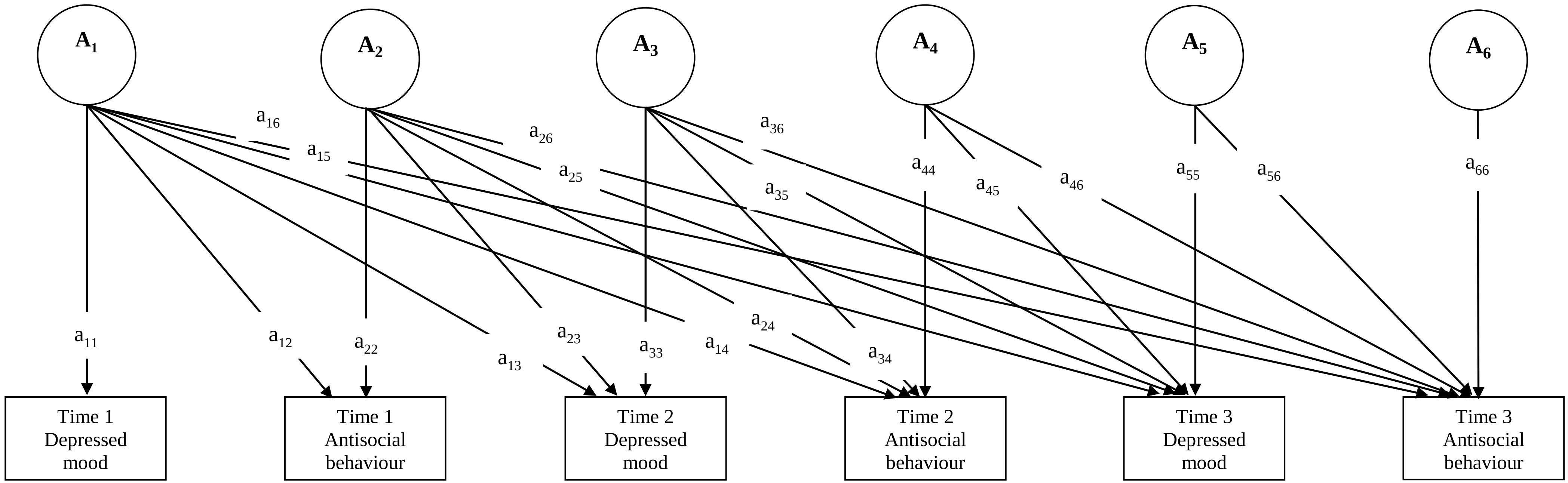

Figure 3.2 Multivariate Cholesky decomposition (A)

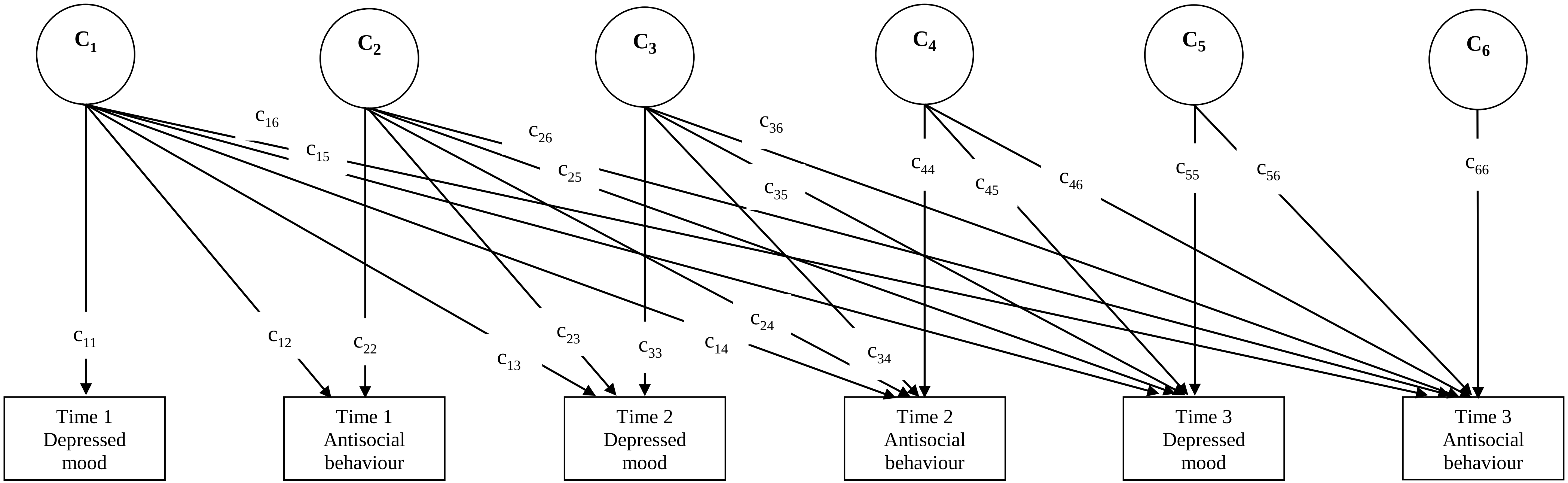

Figure 3.3 Multivariate Cholesky decomposition (C)

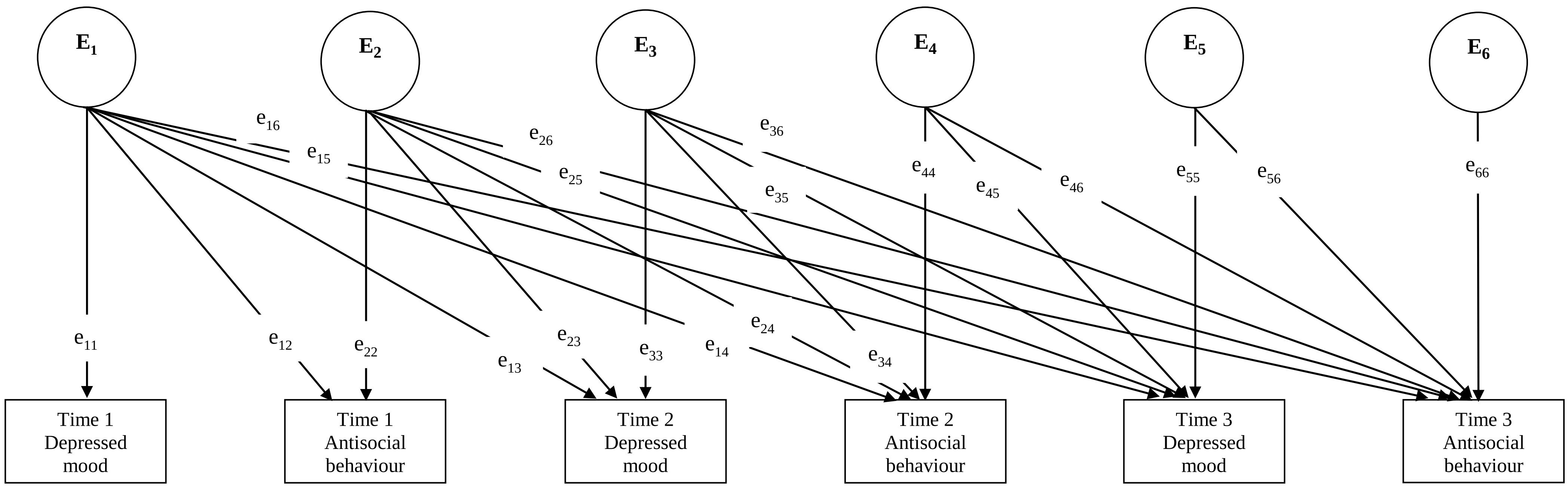

Figure 3.4 Multivariate Cholesky decomposition (E)

Table 3.1 Descriptive statistics on depressed mood and antisocial behaviour

	Total		Male		Female		MZ		DZ		Sib	
	N	M(SD)	N	M(SD)	N	M(SD)	N	M(SD)	N	M(SD)	N	M(SD)
Time 1 DEP	2628	8.08 (6.65)	1152	6.69 (5.51)	1476	9.16 (7.24)	692	7.08 (6.24)	1271	8.08 (6.56)	583	9.37 (7.15)
Time 1 ASB	2623	5.23 (4.08)	1147	5.59 (4.40)	1476	4.94 (3.79)	689	4.79 (3.90)	1266	5.32 (4.14)	586	5.44 (4.11)
Time 2 DEP	1590	6.25 (5.33)	633	5.04 (4.78)	957	7.05 (5.52)	444	5.62 (5.13)	820	8.54 (5.47)	301	6.47 (5.28)
Time 2 ASB	1588	4.13 (3.80)	631	4.58 (4.16)	957	3.84 (3.51)	444	3.75 (3.49)	818	4.50 (4.10)	329	3.64 (3.20)
Time 3 DEP	1549	6.45 (5.73)	596	5.58 (5.30)	953	6.99 (5.92)	417	6.20 (5.61)	769	6.57 (5.75)	329	6.51 (5.90)
Time 3 ASB	1543	3.79 (3.43)	588	4.31 (3.88)	955	3.48 (3.09)	416	3.62 (3.21)	766	3.92 (3.54)	328	3.75 (3.52)

Note: N = number of participant; M = Mean; SD = Standard Deviation. DEP= depressed mood (Short version of Mood and Feeling Questionnaire); ASB= antisocial behaviour (Youth Self Report & Adult Self Report); MZ = monozygotic; DZ = dizygotic; Sib = non-twin sibling pairs. All analyses focus on raw (i.e. untransformed) variables.

Table 3.2 Phenotypic correlations between depressed mood and antisocial behaviour at times 1, 2 and 3

	Time 1 DEP	Time 1 ASB	Time 2 DEP	Time 2 ASB	Time 3 DEP	Time 3 ASB
Time 1 DEP	1					
Time 1 ASB	.42***	1				
Time 2 DEP	.51***	.29***	1			
Time 2 ASB	.28***	.61***	.44***	1		
Time 3 DEP	.39***	.23***	.50***	.25***	1	
Time 3 ASB	.22***	.44***	.27***	.58***	.39***	1

Note: DEP = Depressed mood; ASB = Antisocial behaviour. *p<.05 level; ** p<.01; ***p<.00. All analyses focus on raw (i.e. untransformed) variables

Table 3.3 MZ, DZ and sibling correlations within and across time points for depressed mood and antisocial behaviour

Twin number		Twin 1 / Sibling1					
MZ twins/	Variable	Time 1 DEP	Time 1 ASB	Time 2 DEP	Time 2 ASB	Time 3 DEP	Time 3 ASB
Twin 2	Time 1 DEP	.48***	-				
	Time 1 ASB	.26***	.52***	-			
	Time 2 DEP	.37***	.19***	.40***	-		
	Time 2 ASB	.17**	.41***	.20***	.42***	-	
	Time 3 DEP	.34***	.18***	.22***	.17**	.38***	-
	Time 3 ASB	.15**	.34***	.10	.37***	.18***	.47***
DZ twins/	Variable	Time 1 DEP	Time 1 ASB	Time 2 DEP	Time 2 ASB	Time 3 DEP	Time 3 ASB
Twin 2	Time 1 DEP	.26***	-				
	Time 1 ASB	.17***	.26***	-			
	Time 2 DEP	.16**	.10**	.26***	-		
	Time 2 ASB	.16***	.18***	.16***	.21***	-	
	Time 3 DEP	.11**	.08*	.17***	.11**	.16***	-
	Time 3 ASB	.04	.14***	.13**	.19***	.08*	.20***
Siblings/	Variable	Time 1 DEP	Time 1 ASB	Time 2 DEP	Time 2 ASB	Time 3 DEP	Time 3 ASB
Sibling 2	Time 1 DEP	.27***	-				
	Time 1 ASB	.18***	.22***	-			
	Time 2 DEP	.11	.04	.09	-		
	Time 2 ASB	.11	.14**	.10	.27***	-	
	Time 3 DEP	.19**	.12*	.13	.05	.19**	-
	Time 3 ASB	.15**	.13*	.11	.11	.01	-.07

Note: MZ = monozygotic; DZ = dizygotic. DEP = Depressed mood; ASB = Antisocial behaviour. **p*<.05 level; ** *p*<.01; ****p*<.00. All analyses focus on raw (i.e. untransformed) variables

3.4.2 Phenotypic and twin correlations

There were strong continuities in both antisocial behaviour and depressed mood across time. There were also moderate associations between antisocial behaviour and depressed mood at all three time points (see Table 3.2). Twin correlations are presented in Table 3.3; the magnitude of correlations are considered according to the criteria set out by Cohen (1988), where a correlation of 0.1 is considered small, 0.3 is medium, and 0.5 is large. MZ twin pairs were approximately twice those of DZ twin pairs and siblings, indicative of genetic influence and little shared environment. All MZ correlations were substantially smaller than 1 highlighting the importance of nonshared environment (which may include measurement error). There is also indication of non-additive genetic effects (D) for several of the within trait and cross trait phenotypes associations as the correlations for MZ twins are more than twice DZ correlations.

3.4.3 Univariate model fitting

All univariate model fitting results are shown in Table 3.4. For the univariate results, the contribution of shared environment was small and nonsignificant (see Table 3.5); C was dropped from the model without significant loss of fit. However, genetic influences were retained as dropping these caused a significant loss of fit. Significant moderate genetic influence was evident for all traits at different time points ranging from .38 to .53. There was substantial influence of nonshared environmental factors, ranging from .47 to .62 (see Table 3.4).

Table 3.4 Parameter estimates (including 95% CIs) for best fitting model (AE)

Phenotype	a^2	e^2
Time 1 DEP	.51 (.45 - .57)	.49 (.43 - .55)
Time 1 ASB	.53 (.46 - .59)	.47 (.41 - .54)
Time 2 DEP	.46 (.37 - .54)	.54 (.46 - .63)
Time 2 ASB	.44 (.35 - .52)	.56 (.48 - .65)
Time 3 DEP	.40 (.29 - .49)	.60 (.51 - .71)
Time 3 ASB	.38 (.27 - .49)	.62 (.51 - .73)

Note: a^2 = additive; e^2= non-shared environment. DEP = depressed mood; ASB = antisocial behaviour.

Table 3.5 Fit statistics for univariate genetic model fitting analyses

Variable	Model	-2LL	df	AIC	ΔLL	Δdf	P
Time 1 DEP	Saturated	7125.59	2504	2117.59	-	-	-
	ACE	7202.39	2540	2122.39	76.79	36	<.001
	AE	**7203.60**	**2541**	**2137.59**	**1.21**	**1**	**.27**
	CE	7219.59	2541	2292.14	17.20	1	<.001
Time 1 ASB	Saturated	5733.51	2498	737.51	-	-	-
	ACE	5781.80	2534	713.80	48.29	36	.08
	AE	**5781.80**	**2535**	**711.80**	**-1.70**	**1**	**1**
	CE	5815.95	2535	746.18	3.44	1	<.001
Time 2 DEP	Saturated	4154.44	1524	1106.44	-	-	-
	ACE	4191.60	1560	1071.60	37.16	36	.42
	AE	**4191.60**	**1561**	**1069.60**	**.00**	**1**	**.97**
	CE	4202.43	1561	1080.43	10.82	1	<.001
Time 2 ASB	Saturated	3542.59	1522	498.59	-	-	-
	ACE	3588.45	1558	472.45	45.86	36	.13
	AE	**3588.45**	**1559**	**470.45**	**.00**	**1**	**.96**
	CE	3597.56	1559	479.56	9.10	1	.003
Time 3 DEP	Saturated	4212.60	1474	1264.60	-	-	-
	ACE	4247.16	1510	1227.16	34.56	36	.54
	AE	**4247.16**	**1511**	**1225.16**	**-7.43**	**1**	**1**
	CE	4259.05	1511	1237.05	1.19	1	<.001
Time 3 ASB	Saturated	3195.15	1469	257.15	-		
	ACE	3246.97	1505	236.97	51.82	36	.04
	AE	**3246.97**	**1506**	**234.97**	**-.00**	**1**	**1**
	CE	3260.15	1506	248.15	3.80	1	<.001

Note: All analyses focus on transformed variables and regressed on age and sex. -2LL = -2*(log likelihood); df = degrees of freedom; AIC = Akaike's Information Criterion statistic (calculated as $\chi^2 - 2df$); ΔLL and Δdf = change in log likelihood statistic and corresponding degrees of freedom (computed as the difference in likelihood and df between each model and the saturated model); P = probability Saturated = full model, additive (A), shared environmental (C) and non-shared environmental (E). DEP = depressed mood; ASB = antisocial behaviour. The best models are in bold.

Table 3.6 Fit statistics for multivariate genetic model fitting analyses

Model		-2LL	df	AIC	ΔLL	Δdf	P
1.	Saturated	17882.32	10511	-3139.68	-	-	-
2.	Cholesky ACE	25332.99	11156	3020.99	7450.67	645	<.001
3.	**Cholesky AE**	**25342.41**	**11177**	**2988.41**	**9.42**	**21**	**.98**
4.	Cholesky CE	25415.04	11177	3061.04	82.05	21	<.001

Note: -2LL = -2*(log likelihood); df = degrees of freedom; AIC = Akaike's Information Criterion statistic (calculated as $\chi^2 - 2df$); ΔLL and Δdf = difference in log likelihood statistic and corresponding degrees of freedom (computed as the difference in likelihood and df between each model and the saturated model; P = probability; Saturated = full model, additive (A), shared environmental (C) and non-shared environmental (E). The best models are in bold.

3.4.4 Multivariate model fitting

Multivariate model fit statistics are presented in Table 3.6, and the parameter estimates presented in Figure 3.5 shows the Cholesky decomposition. The traits are ordered with depressed mood prior to antisocial behaviour within each time point, following the approach of Wertz et al. (2015). In this model, the contribution of shared environment was small and nonsignificant; C was dropped without significant loss of fit (see Table 3.6). Genetic influences were retained as dropping these caused a significant loss of fit (for full ACE models please see Appendix D and E).

As specified by the model (Figure 3.5), A_1 included all genetic effects on depressed mood at time 1. A_1 also accounted for 40% (.21 / (.21 + .31)) of the genetic variance in antisocial behaviour at time 1. At time 2, A_1 accounted for 64% (.30 / (.30 + .00 + .17)) of genetic variance in depressed mood and 30% (.14 / (.14 + .19 + .05 + .09)) in antisocial behaviour. A_1 also accounted for 63% (.25 / (.25 + .00 + .01 + .00 + .14)) of genetic effects in depressed mood and 17.5% (.07 / (.07 + .19 + .06 + .04 + .02 + .02)) in antisocial behaviour at time 3. A_2 accounted for the remaining genetic effects on antisocial behaviour at time 1, by specification (60%: .31 / (.21 + .31)), and also contributed to genetic effects in antisocial behaviour at times 2 (40%: .19 / (.14 + .19 + .05 + .09)) and 3 (43%: .19 / (.07 + .19 + .06 + .04 + .02 + .02)). However, A_2 did not contribute significantly to depressed mood at time 2 or 3 with both parameters estimates close to 0. A_3 accounted for the remaining genetic effects on depressed mood at time 2 (36%: 17 / (.30 + .00 + .17)) and also accounted for 10% (.05 / (.14 + .19 + .05 + .09)) of genetic effects in antisocial behaviour and 15% (06 / (.07 + .19 + .06 + .04 + .02 + .02)) of genetic effects in depressed mood at time 3. No other overlapping genetic effects were found from earlier time point predicting later time points (A_4, A_5 & A_6). Significant new time-specific sources of genetic variance were found for antisocial behaviour at time 2 (17%; A_4) but not time 3 (5%; A_6).

Distinct nonshared environmental influences were found across time for E_1 to E_6 (see Figure 3.5). For example, E_1 accounted for all the nonshared environmental effects on depressed mood at time 1 but did not contribute to nonshared environmental effects on later depressed mood but only to antisocial behaviour at time 1 (6%: .03 / (.03 + .45)). E_2 contains all other nonshared environmental effects on antisocial behaviour at time 1 and also contributed to nonshared environmental effects on antisocial behaviour at time 2 (15%: .08 / (.00 + .08 + .04 + .41)) but made no other significant contribution. E_3 contains all other nonshared environmental effects on depressed mood at time 2 and also contributed to nonshared environmental effects on antisocial behaviour at time 2 (7%: .04 / (.00 + .08 + .04 + .41)) and nonshared environmental effects on depressed mood at time 3 (10%: .06 / (.00 + .00 + .06 + .00 + .54)) but made no other significant contribution. The other sources of nonshared environmental variance were specific to trait and time (antisocial behaviour E_4 = 77%; depressed mood E_5 = 90%; antisocial behaviour E_6 = 78%).

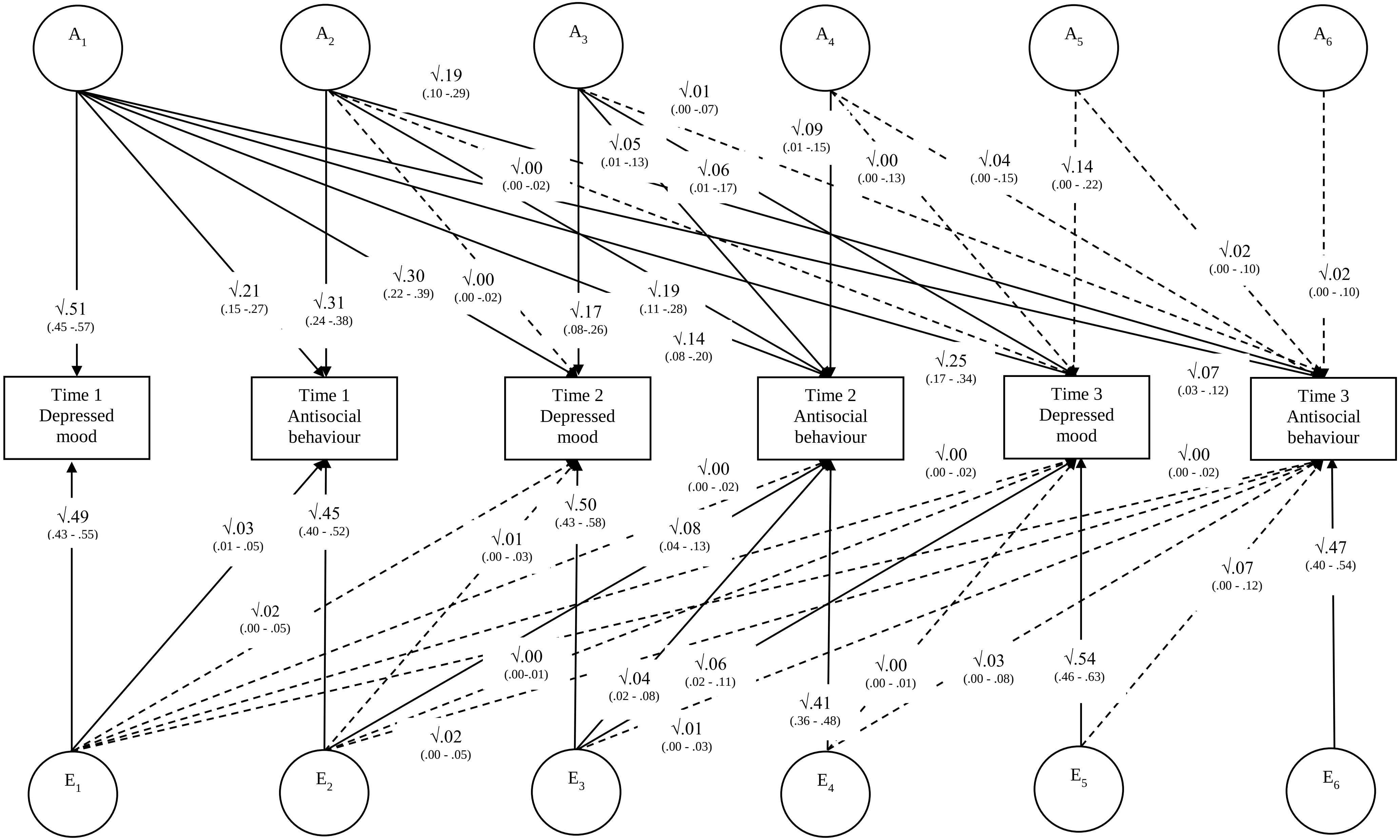

Figure 3.5 Standardised variance estimates from multivariate Cholesky decomposition (including 95% CIs)

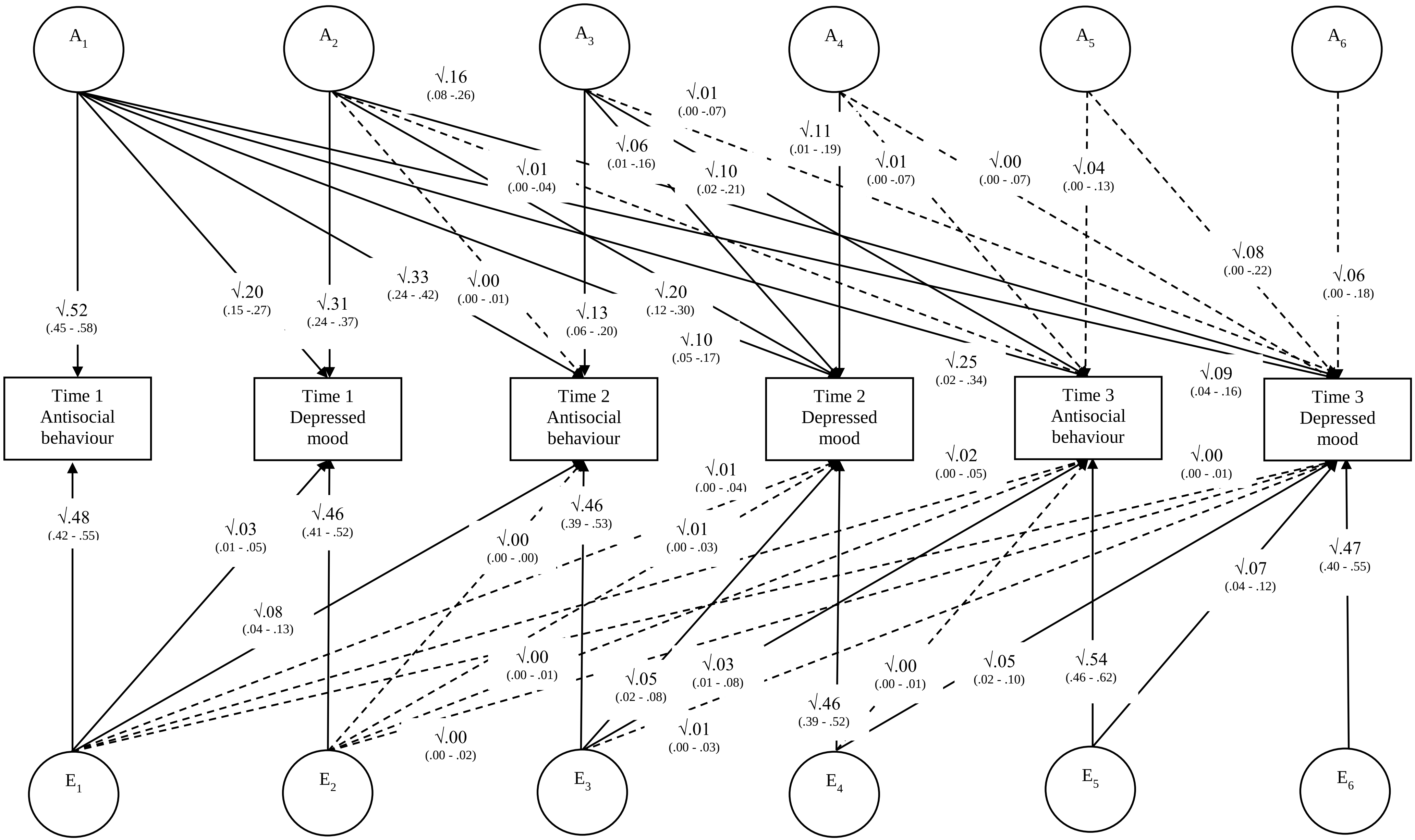

Figure 3.6 Standardised variance estimates from multivariate Cholesky decomposition (including 95% CIs). Re-ordered traits

3.5 Discussion

The present study used a longitudinal genetic design to investigate the association between antisocial behaviour and depressed mood from adolescence to early adulthood. Moderate phenotypic correlations across time indicated stability in antisocial behaviour and depressed mood (Rhee & Waldman, 2002; Rice et al., 2002). As reported elsewhere, both antisocial behaviour and depressed mood were moderately heritable in adolescence and later in adulthood. There were substantial overlaps in the genetic effects supporting the role of generalist genes for antisocial behaviour and depressed mood (Eley, 1997).

3.5.1 Nonshared environmental influence

The nonshared environment accounted for roughly half of the variance in traits studied. Unlike genetic factors, nonshared environmental factors showed little continuity or overlap between traits. The specificity of these nonshared environmental influences may in part reflect time-point specific measurement error. Nonshared environmental effects has previously been reported to account for 43% of antisocial behaviour (Rhee & Waldman, 2002) also accounts for 60% of depression (Sullivan et al., 2000). Overlap in nonshared environmental effects had been previously found between antisocial behaviour and depression account for 25% of the variance (O'Connor, Neiderhiser, et al., 1998). Rowe et al. (2008) found that the nonshared environmental correlation accounted for a small portion of the phenotypic correlation between subscales of antisocial behaviour and depressed mood. However, the current study also found little nonshared environmental overlap between these phenotypes. Nonshared environmental influences have been shown to account for specificity of antisocial behaviour (Burt, McGue, & Iacono, 2010).

3.5.2 Shared environmental influence

There was no shared environmental influence for antisocial behaviour and depressed mood, this was dropped from the model. This may reflect the focus of the sample on adolescence and young adulthood; a number of studies have shown that as individuals age the shared environmental influence plays a less significant role in antisocial behaviour (Jacobson et al., 2002; Moffitt, 2005; Silberg et al., 2007; Tuvblad et al., 2011). The higher rates of shared environmental influence in childhood can also be attributed to artefact of rater bias due to parental reports than child reports (Baker, Jacobson, Raine, Lozano, & Bezdjian, 2007).

3.5.3 Genetic influence

This longitudinal analyses demonstrated continuity of genetic influence on antisocial behaviour and depressed mood across all three time points. New genetic sources of variance came into play at later time points for antisocial behaviour and depressed mood although these new genetic effects did not contribute to the association between phenotypes. This indicates that the genetic effects common to antisocial behaviour and depression are stable over the developmental period studied. This contrasts with findings in younger children. Wertz et al. (2015) showed that 3% of the variance in internalising symptoms in preadolescence was accounted for by genetic effects specific to externalising problems in childhood. Externalising problems in early childhood are more likely to influence new emerging internalising problems in preadolescence. During childhood children are at greater risk of negative experiences including bullying victimisation and conflict with parents as a result of their behaviour (Ball, McGuffin, & Farmer, 2008). Thus, children high in externalising problems exposed to such environments are more likely to develop internalising problems. The current study investigated this effect in adolescence and young adults from the G1219 dataset. The effects of early externalising problems did not lead to new internalising problems later in adulthood. The genetic influence affecting later antisocial behaviour was not already expressed in depressed mood. This does not support the failure model as previous study (Wertz et al., 2015). This study also failed to support the acting out model in that genes from depressed mood were not expressed in antisocial behaviour at later time point. There are a number of potential explanations for the differences in results between the two studies. For example, the age ranges studied by Wertz et al. (2015) spanned childhood to preadolescence where biological, psychological and social change are evident (Smetana, Campione-Barr, & Metzger, 2006). The impact of puberty, relevant to this age-range may play a role in the onset of internalising problems (Angold, Costello, & Worthman, 1998). In contrast, the current study spans adolescence to young adulthood where change in influences on internalising symptoms may be less pronounced.

There may be genes that contribute to risk for both antisocial behaviour and depressed mood through a shared biological disposition. Existing studies provide some guidance on genes that might be candidates to influence both traits. For example, genes involved in the serotonergic systems (e.g. S allele of 5HTTLPR) have been found to increase the risk for both antisocial behaviour and depression (Caspi et al., 2003; Eley et al., 2004; Gunter, Vaughn, & Philibert, 2010). Genetic variation in monoamine oxidase A (MAOA) has also been implicated in both antisocial behaviour and depression in the presence of maltreatment (Byrd & Manuck, 2014; Rivera et al., 2009).

3.5.4 Limitations

Despite the advantages of a large community sample measured over repeated time points, our results must be considered in the context of a number of limitations. The usual limitations applicable to twin studies apply here (Plomin et al., 2013). Twins may differ from singletons on their levels of antisocial behaviour and depression. However, this can be disputed as comparisons between twins and singleton show no major difference in behaviour problems (Johnson et al., 2002; Kendler et al., 1995; Moilanen et al., 1999). Another limitation of this method is the issue of chorionicity which is overlooked with respect to twin samples that address the difference in MZ twin pairs as either sharing or not sharing an amniotic sack (Plomin et al., 2013). However, this limitations may have low effect in different directions (Plomin et al., 2013). Given these limitations, we suggest that genetic and environmental estimates should be considered as indicative instead of absolute.

The use of self-report measures for all traits may have artificially inflated association between measures. Replication using multiple reporters would be beneficial. Assessment method can act as a moderator, for example, previous research has shown that parent reports result in higher correlations than self-report assessment in MZ twins and lower correlations than self-reports in DZ twins (McCartney, Harris, & Bernieri, 1990). Other factors such as age has produced conflicting results, the current study regressed age and sex prior to twin analysis (McGue & Bouchard, 1984). Nonetheless, this study had the advantage of using OpenMx software for use with R which allows for estimation of a wide variety of advanced multivariate statistical modelling. The OpenMx consists of a library of functions and optimizers which allow structural equation models and parameter estimates to be defined quickly and flexibly.

When using longitudinal data, Cholesky decomposition can be used to investigate genetic and environmental influences that are in common and shared between traits at different time points. This method carries the advantage of forming a logical organisation of variables such that factors are constrained to impact later factors but not earlier time points. However, this method does not take into account the time-series nature of the data to see whether the causation is unidirectional across time (Boomsma, Martin, & Molenaar, 1989). Alternative to this method is a simplex model. The simplex model takes account of the longitudinal nature of the data by assessing whether the same genetic and environmental influences affect a trait over time by distinguishing between occasion-specific effects compared to those transmitted from earlier time points. However, this model alone is not sufficient to explain the developmental processes. There was also indication for possibility of non-additive dominance genetic effects (D) for the within and cross trait associations. Future study can investigate this further by adopting a non-additive model (ADE).

Generalisability of these findings poses a limitation as these are based on questionnaire scores, which does not represent the diagnostic criteria for depression and antisocial behaviour. Results can be replicated in clinical samples using different methods of assessments including lifetime diagnostic interviews. There were also variabilities in age range at each time point which makes it difficult to attribute these findings to developmental influences at a specific age or developmental stage. The effects of genetic and environmental influences during each time point are based solely on the mean age of the sample at a particular time point of data collection.

The combined antisocial scale (oppositionality, delinquency and physical aggression) may not have presented the heterogeneity of the effect we observed in the first study. Our approach to measuring the full spectrum of externalising disorder with combined scale allowed comparison to Wertz et al. (2015) data and provided a reliable scale as indicated by Cronbach's alpha. It is possible that subtypes of antisocial behaviour might show a varied pattern of links to depressed mood, however, this might be usefully explored in future work.

3.5.5 Conclusion

Collectively, these findings indicate that there are strong genetic overlaps between antisocial earlier depressed mood carries genetic effects through to antisocial behaviour concurrently, but additional, unique genetic effects also come into play in predicting antisocial behaviour, independent of those shared with earlier depression. The strong phenotypic correlations coupled with strong contemporaneous genetic overlaps are consistent with the possibility that these two phenotypes may share important biological pathways. The shared genetic effects found in this study have important implications for molecular genetics. This leads onto the next chapter for investigating the candidate genes involved in these traits.

Chapter 4 Association study of candidate genes GNβ3 (C825T), 5HTT (5HTTLPR) and COMT ($Val^{158}Met$) with antisocial behaviour and depressed mood

4.1 Overview

The previous chapter indicated that a substantial proportion of the association between antisocial behaviour and depressed mood is genetic in origin. Using twin analyses in the previous chapter for estimating pleiotropy has contributed to molecular genetic analyses in this chapter. This chapter aims to identify some of the genes involved in this association using a molecular genetic approach. The candidate genes investigated involved three functional variants (GNβ3, 5HTTLPR & COMT) in neurotransmitter systems that have previously been associated with either antisocial behaviour or depressed mood. We conducted linear regression analyses using additive, recessive and dominant models of inheritance to test for associations between these polymorphisms and antisocial behaviour and depressed mood. We found a significant association between depressed mood and a polymorphism in GNβ3 (p = .010, recessive model) after adjustment of multiple testing. TT carriers had lower levels of depression scores compared to CT and CC carriers. However, no evidence was found for an association between GNβ3 and antisocial behaviour. Also, no association was found between COMT and 5HTTLPR and both antisocial behaviour and depressed mood. These results failed to show variants which are associated with both traits.

4.2 Introduction

Substantial cross-sectional correlations were reported in the Chapter 2 between antisocial behaviour and depressed mood. Our longitudinal study in the third chapter demonstrated continuity of genetic influences on antisocial behaviour and depressed mood across all three time points. Given the evidence of substantial overlap in the genetic influence accounting for depressed mood and antisocial behaviour from Chapter 3, the next step would be to investigate functional variants (i.e. variants which can alter/influence gene function) of genes in relation to both traits. Although the molecular mechanisms underlying depression and antisocial behaviour are likely complex, there is indication that the serotonergic, dopaminergic, and the noradrenergic pathways are involved in both traits (Bartels et al., 2011; Morley & Hall, 2003; Reif & Lesch, 2003). This chapter investigates the association between three functional variants that are available in the G1219 dataset and that have been previously associated with either antisocial behaviour or depressed mood: GNβ3, SLC6A4 and COMT.

Despite a large body of molecular genetic research on antisocial behaviour and depression, we still know little about the specific genes involved. In genome wide association studies (GWAS) a small number of SNPs (rs16891867, rs1861046, rs7950811, rs11838918) have been found to reach the genome-wide significance for antisocial behaviour (Dick et al., 2011). However, a meta-analysis of GWAS has failed to find any SNPs associated with depression at genome-wide level of significance (Ripke et al., 2013). Despite the power of using GWAS, this approach is not without limitations (Parsons, 2015). GWA studies fail to account for all the heritability associated with a disorder, as identified by twin studies. Furthermore, the causal variant is rarely found which requires functional studies for its validation. There is also a high possibility of false negatives due to the use of stringent multiple testing corrections that lead to high cut-offs (Parsons, 2015).

4.2.1 GNβ3 (C825T)

A variant in the G-protein beta polypeptide 3 (GNβ3) gene plays an important role in transducing transmembrane signalling and regulating secondary messenger pathways for a variety of membrane-bound receptors (Lopez-Leon et al., 2008). A functional polymorphism variant of GNβ3 is rs5443, which results from a cytosine (C) to thymine (T) substitution at position 852 (C852T) within exon 10 of the GNβ3 gene (rs5443) (Siffert et al., 1998). The T (T852) variant is associated with increased signal transduction via the G-protein system and increased cell proliferation (Siffert et al., 1995). The T allele of functional polymorphism (C825T) in the GNβ3 gene has been associated with depression (Fang et al., 2015). A number of studies have reported that depressed patients with T alleles have more severe symptoms of depression and better response to antidepressant treatment (Cao, Hu, Zhang, & Xia, 2007; Fang et al., 2015; Joyce et al., 2003; Lee et al., 2004; Serretti et al., 2003; Wilkie et al., 2007; Zill et al., 2000).

4.2.2 5HTT (5HTTLPR)

The functional polymorphism 5HTTLPR and depression gene is well documented in the literature. There are different allelic forms of this 5HTTLPR polymorphism, a short (S; 14 copies) and a long (L; 16 copies) variant. The S allele of 5HTTLPR has been associated with depression (Collier et al., 1996; Lesch et al., 1996). Numerous research on this polymorphism has focussed on the interaction between the S allele and environmental factors which influence depression (Caspi et al., 2003; Karg et al., 2011; Xia & Yao, 2015). Investigations have also shown that 5HTTLPR polymorphism is a tri-allelic functional polymorphism (A/G, rs25531) in the L allele designated as L_A and L_G with the latter functionally equivalent to the S allele (Hu et al., 2005). The L_G variant has been associated with depression (Zalsman et al., 2006).

In a G1219 study, increased risk of depression for adolescent girls has been found for those with both the SS genotype in addition to environmental risk (Eley et al., 2004). However, some have found no main effect of the 5HTTLPR polymorphism on depression as a result of the effect of genotype being masked by risk of environmental factors. There is significant controversy related to GxE studies including study design (e.g. varying sample size from modest to small, age range variations), timing of measurements (measurements of life events collected in the months preceding depressive outcomes), type of environmental stressors (stressful life events, child maltreatment) and type of outcome (categorical or continuous) (Culverhouse et al., 2013). An additional problem with GxE studies is the lack of control over confounds (e.g. ethnicity, gender, age, socioeconomic status) (Keller, 2014). Many studies have been fraught with methodological and interpretive flaws including inconsistencies in the designated risk genotype(s) and indices of environmental risk across as well as loose standards for replications.

The serotonin transporter has been the target of antidepressant drug therapy (Meyer-Lindenberg et al., 2006; Meyer et al., 2001; Tauscher et al., 1999). Selective serotonin reuptake inhibitors (SSRI) operate by blocking the reabsorption of the neurotransmitter serotonin in the brain, thus changing the balance of serotonin which improves mood (Brigitta, 2002). The L allele is associated with more efficient transcription (Lesch et al., 1994) and better response to SSRI antidepressants (Peters, Slager, McGrath, Knowles, & Hamilton, 2004). Meta-analyses reported that L allele carriers had higher remission and response to SSRI antidepressants than S allele carriers (Karlovic & Serretti, 2013; Porcelli, Fabbri, & Serretti, 2012). However, contradictory findings have been reported by Eley et al. (2012) finding children with anxiety disorders (n = 359) with SS genotype significantly more likely to respond positively to cognitive behaviour therapy than those with SL/LL genotype. At follow up, children with SS genotype were 20% more likely to be free of their primary anxiety disorder diagnosis compared to children carrying LL or SL genotype (78.4% vs. 58.4%). The genetic predictors of differences in individuals in response to psychological treatment is termed as *therapygenetics* which provides important advances in treatment choices which also highlights the importance of using genetic information as a tool for treatment. In another study of poststroke depressed individuals (N = 61), psychosocial intervention was most effective is SS carriers compared to SL and LL carriers (Kohen et al., 2011). Further work is pertinent in this area to form concrete conclusions on the efficacy of therapygenetics and psychological interventions.

Associations between the S allele of 5HTTLPR polymorphism and antisocial behaviour (Lyons-Ruth et al., 2007) and externalising behaviour (Cadoret et al., 2003; Haberstick, Smolen, & Hewitt, 2006; Sakai et al., 2006) have also been reported. For example, Sakai et al. (2006) reported an association between low activity S alleles and CD in adolescents. In a meta-analysis of 18 studies, Frick and Waldman (2014) reported a positive association between the S allele of the 5HTTLPR and antisocial behaviour (*OR* = 1.41, 95% CI = 1.26-1.59). A meta-analysis of GxE which consisted of 8 studies comprising 12 independent samples totalling 7,680 subjects found significant interaction effects of 5HTTLPR and adverse environmental factors (e.g. abuse, adverse childhood events) on antisocial behaviour (Tielbeek et al., 2016). However, no firm conclusions were made on whether the direction of effect is driven by S or L allele or a combination of both (Tielbeek et al., 2016). There is limited research that considers the functional A/G SNP within the 5HTTLPR with depressed mood and antisocial behaviour.

4.2.3 COMT (Val^{158}Met)

The COMT gene produces catechol-O-methyl transferase, which is an enzyme that plays a crucial role in the metabolism of catecholamines including dopamine and norepinephrine by inactivating them in the synaptic cleft and regulating their availability (Gogos et al., 1998; Karoum, Chrapusta, & Egan, 1994; Meyer-Lindenberg et al., 2006). A functional polymorphism of this enzyme is created by the nucleotide substitution of a guanine (G) to adenine (A) mutation in codon 158 (Val^{158}Met: rs4680) which results in amino acid substitution of methionine (Met) for valine (Val) enzyme synthesis. This substitution results in reduction in thermostability and 3-to-4-fold reduction in COMT enzyme activity, which codes for Met instead of Val (Lotta et al., 1995). The Met allele (A) of the enzyme is associated with reduced activity and higher brain dopamine in the prefrontal cortex compared to the Val allele (G) (Lachman et al., 1996). Thus, carriers of Met/Met (AA) variants have the lowest COMT activity, whereas carriers of Val/Val (GG) variants have the highest and Val/Met (GA) (heterozygotes) variants have intermediate levels. The Val allele of the COMT functional polymorphism has been associated with early onset of MDD (Lotta et al., 1995). The Val allele has also been associated with CD (Caspi et al., 2008; DeYoung et al., 2010) and with the risk of antisocial behaviour in individuals diagnosed with ADHD (Caspi et al., 2008).

4.2.4 Polygenic risk scores

Given that multiple genes of small effect size are likely to be involved in depressed mood and antisocial behaviour, studies have focussed on measuring genetic propensity over multiple risky variants in polygenic risk scores (PRS) (Demirkan et al., 2011; Lubke et al., 2012). The PRS can be used to test the predictive power of multiple genetic variants simultaneously. This approach takes into account the joint effects of multiple variants summarised into a single score rather than the effects of individual variants. Antisocial behaviour and depression are both multifactorial polygenic traits influenced by multiple genetic and environmental factors (Bentley et al., 2013; Collins & Sullivan, 2013; Peyrot et al., 2014). For example, a study reported that PRS moderated the effects of childhood maltreatment on depression (Peyrot et al., 2014). The effect of multiple genes has been found to explain around 1-2% of variation in major depression across a number of studies (Demirkan et al., 2011; Ripke et al., 2013; Smoller et al., 2013). There is now a need to see whether PRS can provide information about the overlap between traits. Examining PRS can inform clinical interventions such as pharmacological or psychological treatment (Eley et al., 2012; Keers & Aitchison, 2011; Lester & Eley, 2013).

4.2.5 Aims

Though GWAS allow for an unbiased approach to determining the genetic variation underlying a trait, it is often difficult to determine the functional variant underlying any associations. We instead chose to focus on a small number of functional variants that had been previously associated with either antisocial behaviour or depression. Using the G1219 sample, we sought to investigate the association between GNβ3, 5HTTLPR and COMT with antisocial behaviour and depressed mood. Furthermore, we focussed on functional variants that had been previously implicated in the neurotransmitter systems and that had been associated with either antisocial behaviour or depressed mood. The first stage was to identify the independent associations of each variant with each trait separately followed by examining the polygenic risk score on each trait. If variants were associated with both phenotypes, we planned to examine the extent to which that association may be due to a direct functional effect of the variant on the gene's function. This approach would test if genes involved in both traits account for the comorbidity of the disorders.

4.3 Method

4.3.1 Sample

The sample consisted of twins and siblings from the G1219 longitudinal study, from waves 2, 3 and 4 as outline in Chapter 2 (section 2.3.1).

4.3.2 Measures

Antisocial behaviour. Antisocial behaviour was assessed using 15 items from the Youth Self Report (YSR) (Achenbach, 1991) and Adult Self Report (ASR) (Achenbach & Rescorla, 2003) as outlined in Chapter 2 (section 2.3.2). To create the composite score for antisocial behaviour, the mean of the scores across the three time points was taken (Time 1+ Time 2+ Time 3)/3).

Depressed mood. The short version of the Mood and Feeling Questionnaire (SMFQ) (Angold et al., 1995) measured depressed moods as outlined in Chapter 2 (section 2.3.2). To create the composite score for depressed mood, the mean of the scores across the three time points was taken (Time 1+ Time 2+ Time 3)/3).

4.3.3 Molecular genetics: the basics

DNA consists of genetic information which is required for protein synthesis. This consists of 4 nucleotide bases: adenine (A), cytosine (C), guanine (G), and thymine (T). Pairs are formed between the nucleotides (T with A, G with C) forming a double helix structure consisting of two strands. Genes are organised from segments of these nucleotides which represent the basic unit of heredity. There are two or more forms of genes which are referred to as alleles. Identical alleles represent homozygous genes, whereas non-identical genes are heterozygous. When there are variations in segments of genes this is referred to as polymorphisms. Polymorphisms involving only one nucleotide are referred to as single nucleotide polymorphism (SNP). There are different forms of genetic variation including deletions, insertions and substitutions. Other polymorphisms include length variations, variable number tandem repeats, and duplication.

4.3.4 DNA extraction and genotyping

Cheek swab kits were posted to participants in order to collect DNA (primarily during wave 4 - time 3). Three SNPs were genotyped: 5HTT (rs25531); GNβ3 (rs5443); COMT (rs4680). 5HTTLPR polymorphism alleles were categorised as long (L) or short (S). The A/G allows the distinction between S_A, L_A, and L_G alleles. As the L_G allele is equivalent to the S allele, tri-allelic genotypes were re-categorised into a bi-allelic model according to their expressions as follows: L_GL_G and SL_G were categorised as SS, SL_A and L_GL_A as SL, and L_AL_A as LL. GNβ3 C825T alleles were categorised as C or T. COMT alleles were categorised as A or G. All the genotyping assays were performed by KBioscience (http://www.kbioscience.co.uk) using KASPar chemistry (for more details see: http:// www.lgcgenomics.com/ genotyping/kasp-genotyping-reafgents/kasp-overview/). Blind duplicates and Hardy-Weinberg equilibrium (HWE) tests was used as quality control tests (Barrett, Fry, Maller, & Daly, 2005). Linkage disequilibrium and HWE were calculated using the Haploview program.

4.3.5 Statistical analysis

All the analyses were conducted in Stata (StataCorp, 2007). Mean for antisocial behaviour and depressed mood was created across the three time points (referred to as composite score). We also created a binary variable coded as 1 for individuals that fell above 25% cut-off and 0 for individuals that lay below this for both antisocial behaviour and depressed mood measures (75% cut-off). The same method was used for creating binary variable for 90% cut-off as a sensitivity measure.

Differences in composite scores on measures of antisocial behaviour and depressed mood were first assessed between the sexes using *t*-tests. Linear regression analyses were conducted to model the association of 3 SNPs (GNβ3, 5HTTLPR and COMT) first on 75% cut-off scores followed by stringent measure of 90% cut-off scores and finally the standardised composite scores of antisocial behaviour and depressed mood. Age and sex were first entered into the regression models, followed by genotype. This was followed by analysis of specific time points separately.

We investigated three non-independent models of inheritance: *additive* (each gene copy contributes an equal amount to the phenotype; the relative risk of carrying two copies of the high-risk allele is the square of the risk of carrying one copy) (Lewis & Knight, 2012), *recessive* (requires the presence of two copies of the gene; there is no increased risk associated with carrying one copy of the risk allele, but there is an increased risk associated with carrying two copies) and *dominant* (regulate a phenotype when only one copy of the allele is present; risk of carrying two copies of the risk allele is the same as carrying one copy). As our sample included related individuals, all analyses were corrected for the non-independence of the twin/sibling observation using the "*robust*" option in Stata's regression commands (Rogers, 1994).

We also created polygenic risk scores by taking the sum of risk alleles for each SNP separately for each model of inheritance. As we used the combined time points for both traits, we were able to reduce the risk of false positives being identified due to multiple testing. We also applied a Bonferroni correction to control for multiple testing independently for antisocial behaviour and depressed mood. As three SNPs were investigated, the corrected *p*-values for antisocial behaviour and depressed mood were: $p = .05/3 = .017$. We did not apply corrections for multiple testing for the number of inheritance models that we ran (additive, recessive and dominant), as these tests were not independent of each other.

4.4 Results

4.4.1 Descriptive statistics

The genotype counts and percentages for the 3 SNPs investigated are summarised in Table 4.1 with means and standard deviations for the mean scores of antisocial behaviour and depressed mood by genotype for the total sample for the GNβ3 (rs5443: C825T), 5HT (rs25531: 5HTTLPR) and COMT (rs4680: $Val^{158}Met$). All SNPs were in HWE ($p < .005$) (GNβ3: $\chi^2 = .86$, $p = .35$; 5HTTLPR: $\chi^2 = .10$, $p = .75$; COMT: $\chi^2 = 3.54$, $p = .06$).

There were sex differences for antisocial behaviour (mean = 5.30, SD = 4.13; mean = 4.43, SD = 3.25) for males and females respectively, ($t(2137) = 6.08$, $p < .001$)), with males scoring higher on antisocial behaviour scale than females. Significant sex difference was also found for depressed mood (mean = 6.12, SD = 4.84; mean = 8.27, SD = 5.84), for males and females respectively, ($t(2620) = -10.30$, $p < .001$)), with females showing higher depressed mood scores, we thus controlled for sex in the regression models.

Table 4.1 Genotype frequencies and Mean scores (standard deviation) for antisocial behaviour and depressed mood by genotype

Marker	Genotype	Frequencies (%)	Antisocial behaviour	Depressed mood
GNβ3	CC	466 (49.5)	4.02 (2.62)	7.13 (4.83)
	CT	385 (40.9)	4.60 (3.36)	7.35 (5.11)
	TT	91 (9.6)	4.04 (2.86)	6.22 (4.35)
	Total n	942	942	941
5HTTLPR	LL	279 (25.2)	4.53 (3.11)	7.96 (5.98)
	SL	558 (50.3)	4.50 (3.24)	7.43 (5.48)
	SS	272 (24.5)	4.57 (3.43)	7.10 (5.52)
	Total n	1109	1057	1056
COMT	AA	341 (28.4)	4.21 (3.09)	6.95 (5.31)
	AG	566 (47.2)	4.58 (3.26)	7.95 (5.98)
	GG	292 (24.4)	4.53 (3.31)	6.79 (5.13)
	Total n	1199	1148	1147

Note: n = number; GNβ3 = Guanine nucleotide binding protein beta 3; 5HTTLPR = Serotonin transporter linked promoter region; COMT = Catechol-O-methyl transferase. The 5HTTLPR tri-allelic genotypes based on the A/G SNP within the LPR were re-categorized into a bi-allelic model as follows: L_GL_G and SL_G genotypes were re-categorized as SS; SL_A and L_GL_A as SL; and L_AL_A as LL.

4.4.2 Linear regression results

In the first stage, we looked at 75% cut-off scores, followed by a 90% cut-off and standardised composite scores for antisocial behaviour and depressed mood. Here we report the results separately for each gene on 75% cut-off (see Table 4.2). As results for the 90% cut-off scores and the composite scores were consistent with the 75% cut-off, these are not presented here (see Appendix F and G).

4.4.2.1 GNβ3 (C825T)

A significant association between the rs5443 genotype and the 75% cut-off was found for depressed mood using a recessive model of inheritance (p = .010). This was significant at the Bonferroni-corrected significance level (see Table 4.2 for a summary of the linear regression scores). Sensitivity analyses using a 90% cut-off supported this (see Appendix F). Similar results were found for standardised composite scores for depressed mood (see Appendix G). These results indicate that TT individuals (n = 91, mean = 6.22, SD = 4.35) had lower depressed mood scores than CT and CC individuals (n = 851, mean = 7.23, SD = 4.96) (see Figure 4.1). Results for 90% cut-off scores, composite scores and individual time point scores were consistent with the 75% cut-off, these are not presented here (see Appendix F, G & H).

4.4.2.2 5HTT (5HTTLPR)

The linear regression analyses (see Tables 4.2) revealed no significant association at the Bonferroni corrected level of significance between 5HTTLPR genotype and antisocial behaviour or depressed mood.

4.4.2.3 COMT (Val^{158}Met)

The linear regression analyses (see Table 4.2) revealed no significant association at the Bonferroni corrected level of significance between COMT (rs4680) and antisocial behaviour or depressed mood.

Table 4.2 Standardised regression coefficients (β (SE)) from linear regression analyses for main effects of genotype on composite scores of antisocial behaviour and depressed mood with 75% cut-off

Marker	SNP		Antisocial behaviour	Depressed mood
GNβ3	rs5443	Additive	.06 (.05)	-.05 (.05)
		Recessive	-.07 (.10)	**-.24 (.09)***
		Dominant	.12 (.06)	-.00 (.06)
5HTTLPR	rs25531	Additive	-.01 (.04)	-.05 (.04)
		Recessive	-.04 (.06)	-.09 (.06)
		Dominant	.02 (.06)	-.03 (.07)
COMT	rs4680	Additive	.06 (.04)	.01 (.04)
		Recessive	.04 (.06)	-.08 (.06)
		Dominant	.12 (.06)	.10 (.06)

Note: GNβ3 = Guanine nucleotide binding protein beta 3; 5HTTLPR = Serotonin transporter linked promoter region; COMT = Catechol-O-methyl transferase. SE = standard error. The table presents the standardised repression coefficients for linear regression analyses using additive, recessive and dominant models of inheritance for antisocial behaviour and depressed mood measures. Significant results (following multiple correction) are highlighted in bold type. *Significant results following multiple testing correction (p <.017).

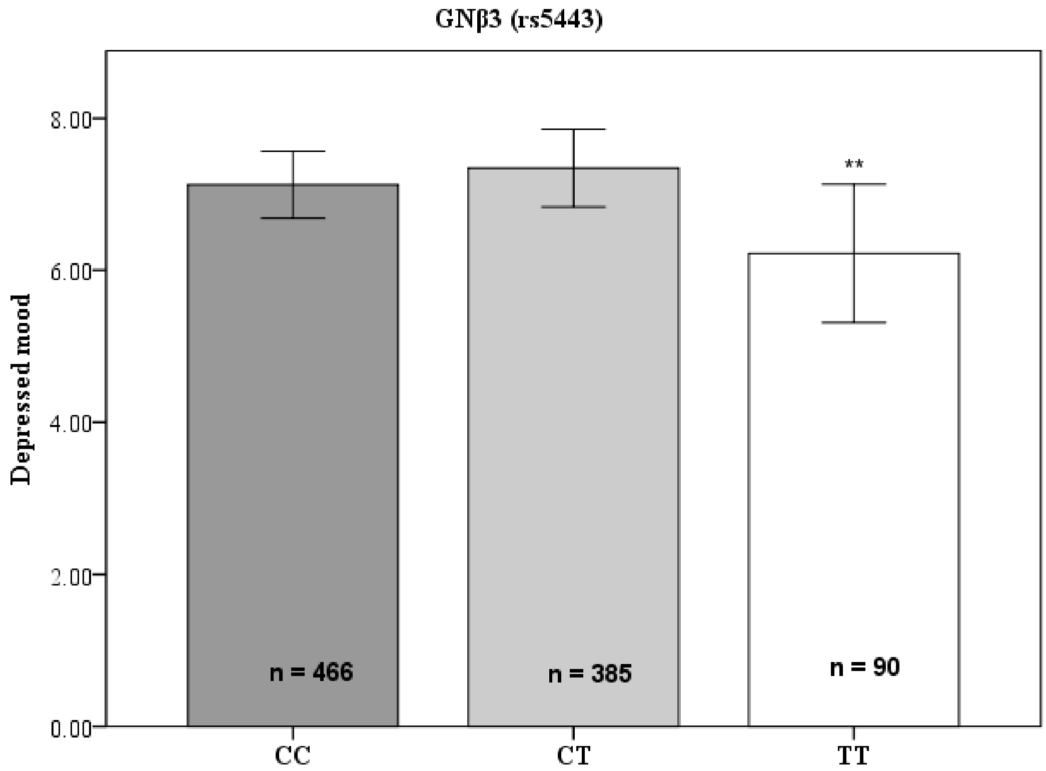

Figure 4.1 Guanine nucleotide binding protein beta 3 (GNβ3) is associated with variations in depressed mood in recessive model.

4.4.3 Polygenic risk scores

The PRS results for combined genes was significantly associated with depressed mood using a recessive model of inheritance (β = -.09, SE = .04, p = .01) reaching the Bonferroni corrected p-value (see Table 4.3). Removal of GNβ3 (rs5443) genotype was carried out to investigate the change in the significant level. The results from the PRS recessive model led to nonsignificant association with depressed mood (β = -.07, SE = .04, p = .07), which show that GNβ3 accounted for the significant results.

Table 4.3 Standardised regression coefficients (β (SE)) from linear regression analyses for main effects of mean PRS on standardised composite scores of antisocial behaviour and depressed mood

PRS	Antisocial behaviour	Depressed mood
Additive	-.02 (.01)	.01 (.01)
Recessive	-.04 (.04)	**-.09 (.04)***
Dominant	-.03 (.02)	-.00 (.02)

Note: PRS= Polygenic risks score (total score across 3 genes); SE = standard error. The table presents the standardised repression coefficients for linear regression analyses using additive, recessive and dominant models of inheritance for antisocial behaviour and depressed mood measures. Significant results (following multiple correction) are highlighted in bold type. *Significant results following multiple testing correction (p <.017).

4.5 Discussion

This study set out to examine the association between GNβ3, 5HTTLPR and COMT functional polymorphisms in the comorbidity between antisocial behaviour and depressed mood. In this study, the focus was on the functional variants that had been previously implicated in the neurotransmitter systems and had been associated with either antisocial behaviour or depressed mood. Before examining the role of these genes in the comorbidity of antisocial behaviour and depressed mood, it was necessary to examine how they related to each forms of psychopathology individually. We found significant association of GNβ3 rs5443 genotype with depressed mood in the recessive model of inheritance using different sensitivity measures. However, no evidence of a significant association between GNβ3 and antisocial behaviour was found. Also, there was no evidence of an association between the 5HTTLPR and COMT polymorphisms and antisocial behaviour or depressed mood. As none of the genes were associated with both antisocial behaviour and depressed mood, there was no evidence that these specific variants contribute to the comorbidity between the two forms of psychopathology.

4.5.1 GNβ3 associated with depressed mood

The significant association of GNβ3 and depressed mood in the recessive model can be due to direct functional effects of the variant on GNβ3 gene's function. PRS results also revealed significant results for depressed mood in the recessive model of inheritance consistent with linear regression analyses. However, removal of this variant from the overall sum of genes resulted in nonsignificant results, which indicates that GNβ3 accounted for the significant results. These results add further support for the involvement of the serotonin neurotransmitter system in depressed mood. However, these findings contradict previous studies which found an association between T allele of GNβ3 rs5443 and depression (Fang et al., 2015). In the meta-analysis conducted by Fang et al. (2015) the frequency of T alleles was significantly higher in depressive patients than that in healthy controls. No association was found between the GNβ3 polymorphism and antisocial behaviour. This was the first study to address this as no previous study has shown any direct link between this variant and antisocial behaviour.

4.5.2 No association between 5HTTLPR and depressed mood / antisocial behaviour

With regards to 5HTTLPR, we found no evidence for a significant association between S allele and depressed mood. The lack of association between this polymorphisms and depressed mood was surprising, as previous studies have reported significant associations. Previous analyses of the G1219 found significant main effect of 5HTTLPR allele with depression in girls based on the selection of the top and bottom 15% of adolescents (N = 377) (Eley et al., 2004). In the present study, a different criterion was included (top 25% and top 10% for the cut-off point). In addition, the current study utilised the tri-allelic functional polymorphism (A/G) in the L allele designated as L_A and L_G, whereas in Eley et al. (2004) study, the bi-allelic forms of 5HTTLPR was adopted. Nonetheless, a meta-analysis has shown significant associations between S allele of 5HTTLPR and the tri-allelic polymorphism and depression (Lopez-Leon et al., 2008; Lotrich & Pollock, 2004). The association of 5HTTLPR and depressed mood may be influenced by environmental risks as shown in previous studies and it is possible that effect of this polymorphism is only found in the presence of environmental risk factors such as stress (Eley et al., 2004).

With regards to antisocial behaviour, no association was found between 5HTTLPR and antisocial behaviour. This also contradicts earlier research including a meta-analysis which reported a significant association between antisocial behaviour and the S allele which was similar across community and clinical population (Ficks & Waldman, 2014). In line with our findings, some studies have found no associations between 5HTTLPR S allele and delinquency and CD (Sakai et al., 2010; Sakai et al., 2007).

4.5.3 No association between COMT and depressed mood / antisocial behaviour

With regards to COMT ($Val^{158}Met$: rs4680), there was no evidence for an association with depressed mood, and the present study did not replicate previous reported findings that the Val allele of the COMT functional polymorphism is associated with early onset of MDD (Lotta et al., 1995). This association was found in a sample with clinical depression. Although the current study represents the top 25% and 10% of the sample, we did assess clinical diagnoses in our study. Despite having a reasonably large sample, it was somewhat small of a candidate gene study and a lack of power may have accounted for the nonsignificant association.

There was also no association between the COMT (Val^{158}Met: rs4680) polymorphism and antisocial behaviour. Contrary to these findings, previous research has shown an association of COMT (Val^{158}Met: rs4680) with antisocial behaviour in individuals diagnosed with ADHD (Caspi et al., 2008). Caspi et al. (2008) focussed on antisocial behaviour in a sample with ADHD, whereas the current study utilised the general population, which may partly explain the discrepancy between the results.

4.5.4 Limitations

The G1219 study is well suited for the purposes of this study as it is a large-scale community sample. Nonetheless, the limitations discussed in Chapter 2 and 3 on the use of self-report measures also apply for this study. A further limitation applicable to this study is the selection of a small number of candidate genes from G1219 dataset. Future work can examine other potential functional variants of candidate genes from different neurotransmitter pathways (e.g. dopaminergic pathway) (Bartels et al., 2011; Morley & Hall, 2003; Reif & Lesch, 2003).

4.5.5 Conclusion

In conclusion, we were able to identify a single genetic polymorphism associated with depressed mood, which further supports the role of the serotoninergic pathways in the neurotransmitter system involved in depressed mood. Further studies are required to uncover the nature of functional polymorphisms in serotonergic and dopaminergic pathway genes and additional genes involved in antisocial behaviour and depressed mood in larger samples and alternative approaches such as GWAS.

This study found that the association between antisocial behaviour and depressed mood may not be influenced by the specific genes examined in this study. We were not able to further investigate the overlapping association between antisocial behaviour and depressed mood at the molecular gene level. Thus, overlapping genetic influences highlighted in previous chapters may not apply to the genetic polymorphisms focused upon in this study. Future work will need to select other possible candidate genes that are associated with both traits from other pathways in the neurotransmitter system (e.g. dopaminergic pathways). We can also move away from candidate gene studies and instead focus on GWAS studies and rare genetic polymorphisms. Future work may also consider gene expression including the role of epigenetics in explaining associations between phenotypes. Both genetic and environmental exposure have been shown to impinge on epigenetic factors. Investigating epigenetic factors in depression and antisocial behaviour may allow an integral view of how genetic and environmental factors alter risk.

Chapter 5 General discussion

5.1 Overview

This thesis aimed to investigate the association between antisocial behaviour and depression from adolescence to adulthood by using longitudinal data. The first study (Chapter 2) investigated the phenotypic association between antisocial behaviour subscales (oppositionality and delinquency) and depressed mood over three time points, to investigate the directional effects of one trait to another. The next step was to investigate the association using behavioural genetic methods in Chapter 3. This focussed on the genetic and environmental influences on the associations between antisocial behaviour and depressed mood across time. Finally, Chapter 4 investigated candidate genes to see whether they accounted for the association in antisocial behaviour and depressed mood. This chapter will cover the main findings across the three studies, limitations, implications for research and future direction.

5.2 Summary of results

Overall, Chapter 2 investigated the first aim of the thesis using phenotypic models to assess the longitudinal associations between antisocial behaviour and depressed mood across different developmental periods using structural equation modelling. Chapter 3 took advantage of twin design to analyse univariate and multivariate models (Cholesky decomposition) to uncover the genetic overlap between both traits longitudinally. Chapter 4 further extended the analyses by examining the role of measured genes in the association of both traits.

5.2.1 Associations between antisocial behaviour and depressed mood

In the first study (Chapter 2), the developmental links between antisocial behaviour and depressed mood was investigated. The heterogeneity of antisocial behaviour was taken into account by assessing the two subscales of antisocial behaviour that had previously been associated with depression (delinquency and oppositionality) at a single wave (Rowe et al., 2006). This chapter investigated autoregressive cross-lagged pathways from three time points. Cross-trait causal paths were also investigated between each trait over time to examine the three developmental models (the failure model, acting out model and mutual reinforcement model). The aim was to investigate longitudinal pathways between traits to uncover the mechanisms involved in the association between antisocial behaviour and depressed mood.

The contemporaneous correlation pathways revealed significant association of both subtypes of antisocial behaviour with depressed mood at each time point. The strong cross-sectional association within each developmental period is in line with past research (Angold et al., 1999; Rowe et al., 2006; Wolff & Ollendick, 2006). While antisocial behaviour and depression represent different symptom characteristics at clinical level, past research has shown comorbidity above chanc level between these traits (Angold et al., 1999). Research from population based samples and clinical samples both support the comorbidity of antisocial behaviour and depression (Beyers & Loeber, 2003; Biederman et al., 1995; Fergusson & Woodward, 2002; Goodyer, Herbert, Secher, & Pearson, 1997). There were no significant differences between subscales of antisocial behaviour in terms of the magnitude of the association with depressed mood. Thus, antisocial behaviour subscales were combined in further analyses.

Autoregressive paths between time points for each trait were significant representing continuities in the behaviour over time. For example, oppositionality from time 1 predicted oppositionality at time 2, and oppositionality at time 3 was predicted from time 2. The significant autoregressive pathways were in line with previous research whereby the same trait is predicted over time (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Past research has shown that children with depression have an increased risk of having depression as adults (Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Pine, Cohen, Gurley, Brook, & Ma, 1998; Rao et al., 1995; Weissman et al., 1999). Similarly, children with CD were more likely to exhibit antisocial behaviour as adults (Weissman et al., 1999).

In addition to uncovering the cross-sectional association, cross-trait developmental associations were investigated using three developmental models (failure, acting out and mutual reinforcement model) (Capaldi, 1992; Capaldi & Stoolmiller, 1999; Carlson & Cantwell, 1980; Overbeek et al., 2001). Cross-trait pathways over time were only significant from depressed mood to oppositionality not vice versa. The findings are most consistent with the acting out model (Carlson & Cantwell, 1980). In line with this model, depressed mood led to oppositionality at different time points (Carlson & Cantwell, 1980). According to the acting out model, externalising behaviours are displayed which uncover internalising problems (Carlson & Cantwell, 1980). The acting out behaviour accompanies the depressive feelings which contribute to masked depression (Benamos, 1992). Depressive behaviour problems are masked by engaging in antisocial behaviour. The findings from this study are consistent with previous studies from adolescence to adulthood (Ritakallio et al., 2008; Wiesner, 2003).

There was no significant pathway between depressed mood and delinquency and vice versa. The findings failed to support the failure model and the mutual reinforcement model. Thus, the contemporaneous association found between antisocial behaviour and depressed mood is not driven by the cross-lagged longitudinal effects.

5.2.2 Genetic influences on the association between antisocial behaviour and depressed mood

Study 2 (Chapter 3) used a longitudinal behavioural genetic design to investigate the association between antisocial behaviour and depressed mood from adolescence to early adulthood using twin analyses to uncover the contribution of new and shared genetic effects on the association. There was moderate shared genetic influence at each time point between antisocial behaviour and depressed mood. Both antisocial behaviour and depressed mood were moderately heritable in adolescence and young adulthood. These support the generalist gene in the view that general genes contribute to both traits (Eley, 1997). Longitudinal continuity of genetic influence was found for antisocial behaviour and depressed mood. Some new genetic sources of variance came into play at later ages for antisocial behaviour and depressed mood although these new genetic effects did not contribute to the association between phenotypes. This indicates that the genetic effects common to antisocial behaviour and depression are stable over the developmental period studied.

5.2.3 Nonshared environmental influences on the association between antisocial behaviour and depressed mood

Nonshared environmental influence represent factors which make siblings different from one another (E) (also includes measurement error). Nonshared environmental influences accounted for a small proportion of the association between antisocial behaviour and depressed mood. This indicates that environmental influences were unique to each trait. The nonshared environment was time-specific with little continuity or overlap between antisocial behaviour and depressed mood, this also includes measurement error. The lack of environmental effects has previously been reported for antisocial behaviour and depressed mood (Rhee & Waldman, 2002). Nonshared environmental influences have been shown to account for specificity of antisocial behaviour (Burt et al., 2010). MZ twin difference design can be used to disentangle the genetic and nonshared environmental influence on the association between antisocial behaviour and depression which has been previously used in different traits (Asbury, Dunn, Pike, & Plomin, 2003; Caspi et al., 2004; Liang & Eley, 2005).

5.2.4 Shared environmental influences on the association between antisocial behaviour and depressed mood

Shared environmental factors represents the influence that makes siblings alike (C). There was no evidence for significant shared environmental influences on antisocial behaviour or depressed mood. As noted by previous reviews, environmental influences are largely nonshared across psychopathology (Plomin, Chipuer, & Neiderhiser, 1994). Large samples are also required to detect shared environmental influences (i.e., at least 7,000 pairs are required for detecting 10% of shared environmental influence) (Martin, Eaves, Kearsey, & Davies, 1978). Shared environmental influence have been predicted to reduce with increasing age whereas genetic effects increase over time (Bergen, Gardner, & Kendler, 2007). Previous studies have found persistent shared environmental influences prior to adulthood with one study finding this effect across ages 3, 7, 10 and 12 (Bartels et al., 2004). The current study focused on the later stages of development involving adolescence and young adults.

A meta-analyses of 450 twin and adoption studies across different phenotypes including internalising and externalising problems was conducted by Burt (2009b), this study found 10-15% of environmental influence in externalising disorders and 12-16% in internalising disorders for children and adolescents. This meta-analysis had excluded adulthood as shared environmental influence is generally found to be nonsignificant during that period (Plomin et al., 2013). This can be explained as the importance of nonshared environmental influence takes over in adulthood for different phenotypes (Plomin et al., 2013). A study has also reported similar effects for the comorbidity between internalising and externalising effects, finding significant effect of genetic and nonshared environmental effects but not shared environmental influence (Cosgrove et al., 2011)

Certain environmental influences which are experienced by both siblings could act to make siblings different from one another such as parental divorce may have a nonshared environmental influence on twins. On the other hand, nonshared environmental influences which are unique to each twin such as negative life events may act in a shared environmental manner making twins within a family more alike (Plomin et al., 2013). It is thus important to investigate the effects of different forms of environmental influences in order to uncover the mechanisms environmental influences take to affect antisocial behaviour and depression.

5.2.5 Association between candidate genes, antisocial behaviour and depressed mood

Given that the second study (Chapter 3) identified overlapping genetic effects between antisocial behaviour and depressed mood, the final study (Chapter 4) set out to examine the association between GNβ3, 5HTTLPR and COMT functional polymorphisms in antisocial behaviour and depressed mood. We found significant association of GNβ3 rs5443 genotype with depressed mood in a recessive model of inheritance meeting the Bonferroni corrected level of significance. However, no evidence of significant association between GNβ3 with antisocial behaviour was found.

Furthermore, no evidence was found for the association between 5HTTLPR and COMT polymorphisms with antisocial behaviour or depressed mood. Past research had shown associations with the selected genes with either antisocial behaviour or depression. However, none of the selected genes in the current sample were associated with both antisocial behaviour and depressed mood, there was no evidence that they contribute to the comorbidity between the two forms of psychopathology. The lack of association can be accounted for by the fact that single genetic variations in these functional genes cannot account for the heritability of the trait in this sample. Thus, the susceptibility of both traits in the current sample may be accounted for by different (and likely larger number) of functional SNPs than currently included in this thesis such as functional variants in the other neurotransmitter pathways (e.g. noradrenergic and dopaminergic pathways).

GWAS had been previously used as an alternative method to candidate gene analysis by simultaneously examining multiple genes in large samples (Stranger et al., 2011). This works by correlating frequencies of alleles at a large number of markers (several hundred thousands) across the genome with trait variation (Stranger et al., 2011). The advantages of GWAS is being unbiased in terms of the genomic structure and prior knowledge of the trait aetiology (Stranger et al., 2011). This has the potential to uncover causal genes that were not previously suspected in disease aetiology in an unbiased way. However, these studies have failed to identify candidate genes associated with disorder and replications have failed across studies and populations (Nebert, Zhang, & Vesell, 2008; Parsons, 2015; Rutter et al., 1998; Salvatore et al., 2015; Stranger et al., 2011). In addition, large sample sizes are required, and the effects of multiple SNPs only explain a small part of an individual's risk for the trait. GWAS also impose a stringent significance level which can be difficult to reach due to weak cumulative predictive power for certain traits (Yngvadottir, MacArthur, Jin, & Tyler-Smith, 2009)

5.2.6 Missing heritability

Missing heritability refers to the genetic loci in association studies which are not sufficient to explain the estimated heritability for complex traits. Despite heritability studies implicating a role for genetic factors, only one genetic variant was associated with one trait in this thesis. GWAS application was hoped to uncover the underlying genetic determinants of psychiatric phenotype heritability (Stranger et al., 2011). However, due to lack of replication of genetic association for complex traits over the past 30 years, and results from GWAS which account for only 1% of the variance in quantitative traits (Park et al., 2011), this has led to missing heritability dilemma (Maher, 2008; Manolio et al., 2009). The missing heritability dilemma is relevant to the findings in this thesis due to the inability to link genetic variants (GNβ3, 5HTTLPR and COMT) with antisocial behaviour and depressed mood. Several explanations have been put forward to account for missing heritability. For example, polymorphisms which are low-frequency or rare are less likely to be captured by genotyping platforms. Secondly, incomplete linkage disequilibrium between causal variants and marker SNPs may result in underestimation of effect size of associated variants. Thirdly, epistasis, epigenetics and GxE contributions to trait heritability may overestimate the heritability.

One possibility is that twin studies overestimate genetic effects because of the equal environment. The equal environment assumption claims that MZ and DZ twin pairs do not differ in the degree of similarity experienced within their environment, if this assumption is violated the heritability is overestimated. Another explanation for the missing heritability in this study can be attributed to the variant itself by being rare in the population.

5.3 Limitations

The G1219 study had a number of advantages for the purpose of this thesis. It was suitable for behavioural genetic analysis and molecular genetic analyses to answer research questions. Despite the strength of G1219, there are a number of limitations across the three studies which are discussed here, whereas specific limitations related to each study are discussed in the specific chapters.

5.3.1 Self-report measures

The current study employed self-report measures to assess antisocial behaviour and depressed mood. The measures used in these studies are widely used for assessing antisocial behaviour and depression and have shown good psychometric properties (Achenbach, 1991; Achenbach & Rescorla, 2003; Angold et al., 1995; Sharp, Goodyer, & Croudace, 2006). Self-report assessment for antisocial behaviour and depression provide valuable information on individual's subjective perception of their own behaviour. It is not clear how the heritability of the estimates and the genetic correlations between different measures would be affected by this. As the current study is longitudinal, the use of multiple informants could mean having different raters at different ages from adolescence to adulthood, as the informants with reliable information on the individual's behaviour may not be the same person at each time point. This also poses another difficulty in increasing confound for the association between the assessments across informants (Tuvblad et al., 2011). Nonetheless, if MZ and DZ twins are affected in similar ways on reporter bias, shared method variance and perceptual bias, then it will be unlikely that these would affect heritability estimates or genetic correlations between measures. Self-reports are useful for measuring antisocial behaviour and depression as it is unlikely that parents of adolescents and younger adults are fully aware of their child's behaviours.

5.3.2 Age

This thesis focused on three time points with mean age for each time point between 15 to 20 years. Studying the period from adolescence to adulthood provides the ability to investigate developmental changes and mechanisms that apply to different stages of development. The three studies in this thesis focus on adolescence to young adulthood, this limits the findings prior to adolescence. Previous studies have reported significant associations in line with the developmental models during childhood to pre-adolescence stage (Wertz et al., 2015). The transition from childhood to adolescence involves biological, psychological and social change (Smetana et al., 2006). For example, puberty may play a role at this stage, which may be important for the onset of internalising problems (Angold et al., 1998).

5.3.3 Twin sample

Despite the advantage of examining the relative contribution of genetic and environmental influences in twin studies, these studies pose a number of limitations. The equal environment assumption holds that trait-relevant environments are equally correlated among MZ and DZ twin pairs in twin studies (Plomin et al., 2013). Violation of the equal environment assumption would be difficult to identify as different environments may decrease or increase the MZ and DZ twins' similarity which can lead to biased parameter estimates. The heritability of a trait would be inflated for example if environments that impact twin similarity in MZ twin pairs are more highly correlated than DZ twin pairs. Researchers have used different methods to assess the plausibility of this assumption including perceived zygosity of twins, physical similarity, parent and twin reports of childrearing. There is limited research to report violation of the equal environment assumption (Kendler, Neale, Kessler, Heath, & Eaves, 1994; Loehlin & Nichols, 1976). To overcome methodological problems of twins reared together, studies have investigated twin-reared apart (Alford, Funk, & Hibbing, 2005). However, these studies also carry a set of problems, biases and environmental confounds (Lewontin, Rose, & Kamin, 1984).

Another limitation of the twin sample is that this is not representative of the general population (Plomin et al., 2013). For a given trait, the twin representative assumption state that twins are representative of the general population. However, it has been argued that twins may not generalise to singletons because they are more likely to experience risk for perinatal complications, perinatal death and lower birth weight (Evans & Martin, 2000). Some critics have reported higher rates of psychopathology among twins compared to singletons (Gau, Silberg, Erickson, & Hewitt, 1992; Gjone & Novik, 1995). However, Kendler (1993) in a review found rates of psychopathology were similar between twins and singletons. These traits have been shown to be generalisable from twins to singletons for depression (Kendler et al., 1995) and delinquency (Barnes & Boutwell, 2013).

5.3.4 Non-clinical sample

The three studies in this thesis used data from G1219, which comprises a non-clinical population of twins and siblings. Previous studies have also used community samples and clinical populations which have both revealed similar trends in the association between antisocial behaviour and depressed mood (Rowe et al., 2006; Rowe et al., 2008). However, in the third study (Chapter 4), we selected the top 25% on our depression and antisocial behaviour measures. To validate these findings, future research can utilise clinical samples to uncover the mechanisms involved in the association.

5.3.5 Attrition

Using longitudinal data and analysing across different time points carries a number of advantages. First, longitudinal data allows us to explore developmental changes (in this case from adolescence to early adulthood) (Card & Little, 2007). Second, longitudinal data provides the ability to investigate the stability and change of behaviour over time. Despite the numerous advantages of longitudinal data, there are some drawbacks to this form of data. The G1219 dataset had 3,640 participants at earlier waves, this was nearly halved over time. A number of reasons could account for the drop out such as lack of interest in further participation, change in circumstances that coincide with later time points. Attrition analyses showed that probability of drop out was greater for children who displayed higher levels of antisocial behaviour. While this may pose a problem to assessing absolute levels of psychopathology in the general population, it is less likely to bias associations between variables (Wolke et al., 2009), which is the focus of this thesis.

5.4 Implications of the current research

The strong overlap between antisocial behaviour and depression over time underscores the importance of examining these overlapping conditions. The association between two distinct but overlapping traits carries implications for understanding aetiology, treatment and disease progression (Biederman et al., 1995). Regarding implication for clinical practice, studying longitudinal association between antisocial behaviour and depression has implications for classification system, aetiology and treatment (Hankin, 2006; Keiley et al., 2003; Overbeek et al., 2001). There is an increase in rates of depression among young people (Murray et al., 2012). Persistent forms of antisocial behaviour place a huge burden on the economy as children from the age of 10 years cost 10 times more than controls by the time they are 28 years old (Scott, Knapp, Henderson, & Maughan, 2001) with burden on families. Targeting adolescents and young adults who manifest symptoms or behaviours of either depression or antisocial behaviour and who are at risk of developing either behavioural problem would be a significant advantage in reducing the rates of mental health and problem behaviour. Understanding mechanisms and the causes for the association can aid in earlier diagnosis or reduction of risk.

5.5 Direction for future work

Despite finding an overlapping association between antisocial behaviour and depressed mood, more work is required to investigate the precise mechanisms underlying the findings.

5.5.1 Molecular genes

The current study focused on functional variants of three genes (GNβ3, 5HTTLPR, COMT) that had been previously associated with either antisocial behaviour or depressed mood. As many genes of small effects influence both antisocial behaviour and depression, future work can investigate more functional variants to identify whether there are overlaps between antisocial behaviour and depressed mood. The current thesis focussed on candidate genes in the serotonergic pathways, future work could be extended to examine genes in other pathways including the dopaminergic pathways. For example, dopamine receptor genes (DRD1, DRD2, DRD4) have been associated with either antisocial behaviour or depression (Corrales, Navarro, Cuenca, & Campos, 2016; Windhorst et al., 2015). Susceptibility genes interacting with developmental factors, epigenetic DNA modification, and stochastic mechanisms may lead to different forms of behaviours (Glazier, Nadeau, & Aitman, 2002; Petronis, 2001).

5.5.2 Epigenetics

Epigenetics may play a role in the association of antisocial behaviour and depressed mood. Production of stable changes in DNA expression (methylation) and chromatin structure that are not the result of changes in DNA sequence are referred to as epigenetics (Henikoff & Matzke, 1997; Jiang, Bressler, & Beaudet, 2004). Individual differences in gene expression have been shown to be predicted by differences in DNA methylation (Bell et al., 2011). Epigenetics provides a different route for explaining the association between antisocial behaviour and depression, which seeks to explain how nurture shapes nature (Powledge, 2011). These occur at a higher frequency than mutation in the DNA sequence and are reversible (McGowan & Szyf, 2010). This provides possibilities for correcting early disadvantages in behaviour problems (Loi, Del Savio, & Stupka, 2013; Tremblay & Szyf, 2010). Epigenetic research has been reported in MDD to explain the mechanisms for the link between the long term effects of adverse life events and change in gene expression (Dalton, Kolshus, & McLoughlin, 2014). As both antisocial behaviour and depression are highly heterogeneous, encompassing a spectrum of symptoms, epigenetics would be an ideal approach to focus on the interplay between genetic and environmental factors on their association (Mill & Petronis, 2007; Schroeder, Krebs, Bleich, & Frieling, 2010).

The G1219 study has investigated epigenetics (specifically DNA methylation) in depression. Dempster et al. (2014) investigate epigenetic variation in 18 MZ twin pairs discordant for depression symptoms, by examining genome-wide patterns of DNA methylation from MZ twin pairs. Buccal cell DNA methylation were identified for 440,000 sites but no significant difference was found between twin pairs in overall mean genomewide DNA methylation. However, significant difference was observed for individual sites, with higher variance for individual with depression (53%) compared to their co-twin control group. Depression-associated differentially methylated probes (DMP) were identified at the top-ranked DMP located in STK32C. The large variance found indicates variabilities in DNA methylation in individuals with depression. Cerebellar methylation was also investigated in postmortem cerebellum in MDD patients and control. Similar sites that were found in the twin study was also significantly associated with MDD in postmortem cerebellum DNA.

5.6 Conclusions

The large-scale sample of twins and siblings in the G1219 study was well placed for investigating the association between antisocial behaviour and depressed mood over multiple time points using quantitative, behavioural genetics and molecular genetic techniques to assess the stability and longitudinal associations. The three studies in this thesis collectively demonstrate that antisocial behaviour and depressed mood are strongly associated. The G1219 sample is in the early stages of adulthood and is continuing to follow the development of behaviour over time to understand gene-environment interplay. Further research could extend to later adulthood and older age groups to examine the consistency in the pattern of results reported in this thesis as well as investigating potential shared risk factors. Further work in epigenetics on the association of depression and antisocial behaviour would be ideal.

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Appendices

Appendix A: Short Mood and Feeling Questionnaire (SMFQ)

Appendix B: Antisocial behaviour scales

Appendix C: Odds ratio for predicting dropout rate for depressed mood and antisocial behaviour

Appendix D: Standardised variance estimates from multivariate Cholesky decomposition (including 95% CIs) – Model 1

Appendix E: Standardised variance estimates from multivariate Cholesky decomposition (including 95% CIs) – Model 2

Appendix F: Standardised regression coefficient (β (SE)) from linear regression analyses for main effects of genotype on composite scores of antisocial behaviour and depressed mood with 90% cut-off

Appendix G: Standardised regression coefficient (β (SE)) from linear regression analyses for main effects of genotype on standardised composite scores of antisocial behaviour and depressed mood

Appendix H Standardised regression coefficient (β (SE)) from linear regression analyses for main effects of genotype on standardised scores of individual time points for antisocial behaviour and depressed mood

Appendix A Short Mood and Feeling Questionnaire (SMFQ)

Item	Description
1	I felt miserable or unhappy
2	I didn't enjoy anything at all
3	I felt so tired, I just sat around and did nothing
4	I was very restless
5	I felt I was no good any more
6	I cried a lot
7	I found it hard to think properly or concentrate
8	I hated myself
9	I felt I was a bad person
10	I felt lonely
11	I thought that nobody really loved me
12	I thought I could never be as good as others
13	I did everything wrong

Appendix B Antisocial behaviour scales

Item	Wave 2	Wave 3	Wave 4
1	I argue a lot	I act too young for my age	I argue a lot
2	I worry what others think	I argue a lot	I use drugs
3	I am mean to others	I brag	I get upset too easily
4	I destroy my things	I often volunteer to help other	I have trouble managing money
5	I destroy things belonging to other people	I am mean to others	I am too impatient
6	I would rather be alone than with others	I destroy things belonging to others	I lie or cheat
7	I disobey my parents	I destroy my own things	I express my feelings too openly
8	I try to conceal personal habits	I day-dream a lot	I am mean to others
9	I am disobedient at school	I have trouble concentrating	I drive too fast
10	I don’t feel guilty	I tease others a lot	My relations with neighbours are poor
11	I try to be nice to others	I hang around with others who get into trouble	My moods swing between elation and depression
12	I get into many fights	I talk too much	I damage or destroy my things
13	I feel ashamed of body	I lie or cheat	I don’t get along well with other people
14	I hang around kids who get into trouble	I physically attack people	I don’t feel guilty after doing something I shouldn’t
15	I lie or cheat	I usually share with others	My moods or feelings change suddenly

16	I have one good friend or more	I scream or yell a lot	I get along badly with my family
17	I physically attack people	I am kind to younger children	I do not show my emotions to others
18	I would rather be with older kids	I try to get a lot of attention	My Behaviour is irresponsive
19	I worry about what others think of me	I show off or clown	I hand around with people who get into trouble
20	I run away from home	I get into many fights	I am impulsive or act without thinking
21	I steal from home	I have a hot temper	I am concerned about the feeling of others
22	I feel ashamed or sort of person I am	My mood or feelings change suddenly	My work performance is poor
23	I usually share with others	I am helpful if someone is hurt or upset	I am very expressive and emotional
24	I scream a lot	I threaten to hurt people	I do not care about doing things well
25	I set fires	I am louder than others	I physically attach people
26	I steal from places other than home	I have trouble standing still	I do not care if I get into trouble
27	Worry about what others think of me	I feel confused or in a fog	I am stubborn, sullen or irritable
28	Others generally like me	I act without stopping to think	I damage things belonging to others
29	I think about sex too much	I am poorly coordinated or clumsy	I drink too much alcohol or get drunk
30	I feel ashamed of ability	I run away from home	I do things that may cause

			me trouble with the law
31	I have a hot temper	I set fires	I steal
32	I tease others a lot	I steal at home	I do not care who I hurt to get what I want
33	I am helpful if someone is hurt	I disobey at school	I have a hot temper
34	I swear a lot	I steal from places other than home	I threaten to hurt people
35	I threaten to hurt people	I am jealous of others	I like to try new things
36	I worry about what others think	I am considerate of other people's feelings	I fail to pay my debts
37	I use alcohol or drugs	I don't feel guilty after doing something I shouldn't	I stay away from my job
38	Other people pick on or bully me	I would rather be with older people than my own age	I fail to finish the things I should do
39	I cut classes or miss school	I am nervous or tense	I break rules at work or elsewhere
40	I avoid looking at myself in mirror	I swear or use dirty language	My relations with the opposite sex are poor
41	I brag	I cut classes and skip school	My behaviour is very changeable
42	I try to get attention	I get along badly with my family	I blame others for my problems
43	I am kind to younger children	I fail to pay my dents or meet financial responsibilities	I get into many fights
44	I am jealous of others	I don't get along well with other people	I scream or yell a lot
45	I scream a lot	I drink too much alcohol	I rush into things without

		or get drunk	considering the risks
46	Not feeling ashamed when failing at school	I fail to finish things I should do	I have trouble planning for the future
47	I show off or clown around people	I am stubborn, sullen or irritable	I do not feel remorseful when I do something wrong
48	I am stubborn	I feel others are out to get me	I have trouble making or keeping friends
49	I volunteer to help others	My behaviour is irresponsible	I hide my feelings from others
50	My mood/feelings change suddenly	I do things that may cause me trouble with the law	I would rather be alone than with others
51	I talk too much	I use alcohol or drugs for non-medical purposes	It is easy for others to tell how I am feeling
52	I want to hide or conceal body	I break rules at school, work or elsewhere	The feelings of others are unimportant to me
53	I am louder than other kids	I am dependent on others	
54	I get on better with adults	I get teased a lot	
55	I feel ashamed when I say something	I am suspicious	

Appendix C Odds ratio for predicting dropout rate for depressed mood, oppositionality and delinquency

Model	Variable	*B*	*SE*	*p*	*OR*	95% *CI* for *OR*
Predicting Depressed mood at Time 2						
Model 1	Depressed mood Time 1	.04	.04	.306	1.04	.96 – 1.13
Model 2	Sex	-.46	.08	.000	.634	.54 – .74
	Age	.07	.02	.005	1.07	1.02 – 1.12
	Depressed mood Time 1	.08	.04	.068	1.08	.99 – 1.17
Predicting Depressed mood at Time 3						
Model 1	Depressed mood Time 2	.09	.06	.121	1.09	.97– 1.22
Model 2	Sex	-.39	.12	.001	.678	.53 – .86
	Age	-.04	.04	.249	.958	.89 – 1.03
	Depressed mood Time 2	.13	.06	.034	1.13	1.01 – 1.27
Predicting Oppositionality at Time 2						
Model 1	Oppositionality Time 1	.12	.04	.003	1.25	1.04 – 1.22
Model 2	Sex	-.45	.08	.000	.640	.55 – .75
	Age	.07	.02	.002	1.08	1.03 – 1.13
	Oppositionality Time 1	.14	.04	.000	1.15	1.06 – 1.25

Predicting Oppositionality at Time 3						
Model 1	Oppositionality Time 2	.37	.06	.000	1.44	1.29 – 1.61
Model 2	Sex	-.38	.12	.002	.682	.54 – .86
	Age	-.03	.04	.484	.974	.91 – 1.05
	Oppositionality Time 2	.34	.06	.000	1.40	1.26 – 1.57
Predicting Delinquency at Time 2						
Model 1	Delinquency Time 1	.25	.04	.000	1.29	1.19 – 1.39
Model 2	Sex	-.38	.08	.000	.686	.59 – .81
	Age	.06	.02	.017	1.06	1.01 – 1.11
	Delinquency Time 1	.22	.04	.000	1.25	1.15 – 1.35
Predicting Delinquency at Time 3						
Model 1	Delinquency Time 2	.19	.06	.000	1.22	1.09 – 1.40
Model 2	Sex	-.31	.12	.011	.735	.58 – .93
	Age	-.04	.04	.283	.961	.89 – 1.03
	Delinquency Time 2	.17	.06	.000	1.19	1.17 – 1.33

Note. Models 1 provide the unadjusted odds ratio for depressed mood predicting later depressed mood and antisocial behaviour predicting later antisocial behaviour. Models 2 provide the odds ratios after controlling for covariates (sex and age). *B* = coefficient; *SE* = Standard Error of *B*; *p* = significance level; *OR* = odds ratio; *CI* = confidence intervals. Sex coded as: 1 = female; 2 = male. Coding: Attended = 0, Not attended = 1.

Appendix D Standardised variance estimates from multivariate Cholesky decomposition (including 95% CIs) – Model 1

	Time 1 DEP			Time 1 ASB			Time 2 DEP			Time 2 ASB			Time 3 DEP			Time 3 ASB		
	A_1	C_1	E_1	A_2	C_2	E_2	A_3	C_3	E_3	A_4	C_4	E_4	A_5	C_5	E_5	A_6	C_6	E_6
Time 1 DEP	.41 (.27-.53)	.09 (.01-.19)	.50 (.44-.57)															
Time 1 ASB	.16 (.07-.28)	.04 (.00-.12)	.03 (.01-.06)	.31 (.20-.38)	.00 (.00-.07)	.46 (.40-.52)												
Time 2 DEP	.41 (.24-.52)	.00 (.00-.09)	.02 (.00-.04)	.00 (.00-.04)	.05 (.00-.15)	.00 (.00-.02)	.01 (.00-.17)	.00 (.00-.14)	.51 (.44-.59)									
Time 2 ASB	.12 (.04-.24)	.02 (.00-.11)	.00 (.00-.02)	.23 (.11-.36)	.03 (.00-.12)	.07 (.04-.12)	.01 (.00-.16)	.00 (.00-.11)	.05 (.02-.08)	.05 (.00-.13)	.00 (.00-.07)	.42 (.37-.48)						
Time 3 DEP	.31 (.16-.43)	.00 (.00-.05)	.00 (.00-.02)	.00 (.00-.04)	.00 (.00-.09)	.00 (.00-.01)	.04 (.00-.22)	.00 (.00-.10)	.05 (.02-.10)	.05 (.00-.21)	.00 (.00-.09)	.00 (.00-.01)	.00 (.00-.21)	.00 (.00-.09)	.55 (.46-.63)			
Time 3 ASB	.10 (.03-.21)	.00 (.00-.05)	.00 (.00-.01)	.20 (.08-.35)	.00 (.00-.08)	.01 (.00-.05)	.02 (.00-.22)	.00 (.00-.08)	.01 (.00-.03)	.08 (.00-.19)	.00 (.00-.06)	.04 (.01-.08)	.00 (.00-.11)	.00 (.00-.06)	.07 (.03-.11)	.00 (.00-.09)	.00 (.00-.05)	.47 (.40-.54)

Note: The results represent squared standardised parameter estimates**:** a^2 = additive; e^2= non-shared environment; e^2= non-shared environment; DEP = depressed mood; ASB = antisocial behaviour.

Appendix E Standardised variance estimates from multivariate Cholesky decomposition (including 95% CIs) –Reordered traits

	Time 1 ASB			Time 1 DEP			Time 2 ASB			Time 2 DEP			Time 3 ASB			Time 3 DEP		
	A_1	C_1	E_1	A_2	C_2	E_2	A_3	C_3	E_3	A_4	C_4	E_4	A_5	C_5	E_5	A_6	C_6	E_6
Time 1 ASB	.47	.04	.49															
	(.34-.56)	(.00-.13)	(.42-.56)															
Time 1 DEP	.14	.08	.03	.27	.01	.47												
	(.06-.24)	(.00-.19)	(.01-.06)	(.16-.35)	(.00-.10)	(.42-.54)												
Time 2 ASB	.35	.00	.08	.00	.05	.00	.06	.00	.46									
	(.20-.49)	(.00-.11)	(.04-.13)	(.00-.02)	(.00-.12)	(.00-.01)	(.00-.17)	(.00-.11)	(.40-.53)									
Time 2 DEP	.15	.01	.01	.26	.04	.01	.00	.00	.05	.01	.00	.46						
	(.06-.29)	(.00-.12)	(.00-.03)	(.09-.39)	(.00-.17)	(.00-.03)	(.00-.12)	(.00-.14)	(.03-.09)	(.00-.13)	(.00-.08)	(.39-.53)						
Time 3 ASB	.30	.00	.02	.00	.00	.00	.10	.00	.05	.00	.00	.00	.00	.00	.53			
	(.18-.43)	(.00-.05)	(.00-.04)	(.00-.04)	(.00-.08)	(.00-.01)	(.00-.23)	(.00-.08)	(.02-.09)	(.00-.10)	(.00-.06)	(.00-.01)	(.00-.11)	(.00-.06)	(.46-.61)			
Time 3 DEP	.10	.00	.00	.21	.00	.00	.02	.00	.01	.07	.00	.05	.00	.00	.07	.00	.00	.47
	(.03-.20)	(.00-.07)	(.00-.01)	(.09-.33)	(.00-.09)	(.00-.02)	(.00-.20)	(.00-.10)	(.00-.03)	(.00-.21)	(.00-.10)	(.02-.09)	(.00-.21)	(.00-.09)	(.04-.12)	(.00-.17)	(.00-.08)	(.40-.56)

Note: The results represent squared standardised parameter estimates**:** a^2 = additive; c^2= shared environment; e^2= non-shared environment; ASB = antisocial behaviour; DEP = depressed mood.

Appendix F Standardised regression coefficient (β (SE)) from linear regression analyses for main effects of genotype on composite scores of antisocial behaviour and depressed mood with 90% cut-off

Marker	SNP		Antisocial behaviour	Depressed mood
GNβ3	rs5443	Additive	.05 (.03)	-.02 (.04)
		Recessive	-.05 (.06)	**-.12 (.06)**
		Dominant	**.11 (.04)**	.01 (.04)
5HTTLPR	rs25531	Additive	.03 (.03)	-.05 (.03)
		Recessive	.04 (.04)	-.08 (.04)
		Dominant	.05 (.04)	.06 (.05)
COMT	rs4680	Additive	.03 (.02)	.02 (.02)
		Recessive	.02 (.04)	-.03 (.04)
		Dominant	.05 (.04)	.07 (.04)

Note: GNβ3 = Guanine nucleotide binding protein beta 3; 5HTTLPR = Serotonin transporter linked promoter region; COMT = Catechol-O-methyl transferase. SE = standard error. The table presents the standardised repression coefficients for linear regression analyses using additive, recessive and dominant models of inheritance for antisocial behaviour and depressed mood measures. Significant results are in bold.

Appendix G Standardised regression coefficient (β (SE)) from linear regression analyses for main effects of genotype on standardised composite scores of antisocial behaviour and depressed mood

Marker	SNP		Antisocial behaviour	Depressed mood
GNβ3	rs5443	Additive	.06 (.04)	-.03 (.04)
		Recessive	-.06 (.09)	**-.21 (.08)**
		Dominant	.12 (.05)	.02 (.06)
5HTTLPR	rs25531	Additive	.01 (.04)	-.07 (.05)
		Recessive	.02 (.07)	-.08 (.07)
		Dominant	-.01 (.06)	-.10 (.08)
COMT	rs4680	Additive	.05 (.04)	-.00 (.04)
		Recessive	.03 (.06)	-.14 (.06)
		Dominant	.09 (.06)	.12 (.07)

Note: GNβ3 = Guanine nucleotide binding protein beta 3; 5HTTLPR = Serotonin transporter linked promoter region; COMT = Catechol-O-methyl transferase. SE = standard error. The table presents the standardised repression coefficients for linear regression analyses using additive, recessive and dominant models of inheritance for antisocial behaviour and depressed mood measures. Significant results are in bold.

Appendix H Standardised regression coefficient (β (SE)) from linear regression analyses for main effects of genotype on standardised scores of individual time points for antisocial behaviour and depressed mood

			Antisocial behaviour			Depressed mood		
Marker	SNP		Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
GNβ3	rs5443	Additive	.02 (.04)	.02 (.05)	**.15 (.05)**	-.03 (.05)	.02 (.05)	-.04 (.05)
		Recessive	-.13 (.10)	-.03 (.11)	.10 (.12)	-.18 (.09)	-.12 (.11)	**-.22 (.11)**
		Dominant	.07 (.06)	.04 (.07)	**.27 (.07)**	.01 (.06)	.08 (.07)	.00 (.07)
5HTTLPR	rs25531	Additive	.01 (.04)	.02 (.05)	-.02 (.05)	-.08 (.05)	.01 (.05)	-.07 (.05)
		Recessive	.01 (.07)	.03 (.08)	-.02 (.08)	-10 (.08)	.02 (.08)	-.13 (.07)
		Dominant	.01 (.07)	.02 (.07)	-.03 (.08)	-.11 (.08)	-.01 (.09)	-.05 (.08)
COM	rs4680	Additive	**.08 (.04)**	-.00 (.04)	.06 (.04)	-.00 (.04)	.01 (.04)	.03 (.05)
		Recessive	.10 (.07)	-.07 (.07)	.02 (.07)	-.13 (.07)	-.12 (.07)	-.03 (.07)
		Dominant	.11 (.06)	.08 (.07)	.13 (.07)	.11 (.07)	.13 (.07)	.10 (.07)

Note: GNβ3 = Guanine nucleotide binding protein beta 3; 5HTTLPR = Serotonin transporter linked promoter region; COMT = Catechol-O-methyl transferase. SE = standard error. The table presents the standardised repression coefficients for linear regression analyses using additive, recessive and dominant models of inheritance for antisocial behaviour and depressed mood measures. Significant results are in bold.