Effects of brain-derived neurotrophic factor and catechol-*O*-methyltransferase genes on cognition

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Abstract

Cognitive abilities demonstrate considerable heritability and the mapping of the human genome has facilitated research into the specific genes that may underlie individual differences in performance. The genes coding for brain-derived neurotrophic factor (BDNF) and catechol-*O*-methyltransferase (COMT) are considered to be likely candidates for impacting on brain structure, function and plasticity, as well as various cognitive abilities. Research on their effects has yielded notoriously inconsistent results, however. Inconsistencies may be in part due to conflated outcome measures and the presence of moderating variables.

The overarching aim of this thesis was to further understanding of the effects of genetic variation in the *BDNF* and *COMT* genes on cognitive outcomes. In the first study, the *BDNF* val^{66}met (Rs6265) and *COMT* val^{158}met (Rs4680) polymorphisms were examined in relation to recall and recognition performance in young adults. Recall and recognition were assessed using the Family Pictures and Faces subtests of the Wechsler Memory Scale – Third Edition (WMS-III), respectively. The *BDNF* polymorphism was demonstrated to affect performance on the hippocampal-dependent recall task while not affecting recognition performance. This indicates the importance of distinguishing between neurologically distinct forms of memory when investigating the effects of genes on memory ability. In the second study, sample size was increased in order to test for sex-specific effects of the *COMT* val^{158}met polymorphism on face recognition. This study revealed an interaction between sex and *COMT* genotype on face recognition performance. *COMT* genotype affected face recognition ability in male participants only. Sex differences were observed for val homozygotes, with female val/val participants scoring significantly higher scores than males of this genotype. In the third study, the personality trait of Conscientiousness was shown to moderate the relationship between the *BDNF* val^{66}met polymorphism and recall performance.

The *BDNF* met allele was only associated with poorer recall performance in individuals low in self-reported Conscientiousness. Conscientiousness predicts a range of health-related behaviours that may bolster hippocampal function in *BDNF* met allele carriers. The fourth study analysed data from the longitudinal Auckland Birthweight Collaborative (ABC) study to examine how exposure to antenatal maternal stress affects the relationship between genetic variants in the *COMT* gene and IQ performance in children. A gene-environment interaction was found. Children exposed to high maternal antenatal stress were demonstrated to have significantly lower full-scale IQ scores at both 7 and 11 years of age than those exposed to low stress, only when they were carriers of the *COMT* Rs165599 G allele. The Rs165599 polymorphism may thus confer differential susceptibility to negative cognitive outcomes following exposure to an early stressor, highlighting the need to consider gene-environment interactions when investigating effects of antenatal stress on cognition. Gene-sex and gene-environment interactions can be obscured in analyses that only allow for main effects of candidate genes on cognition, with implications for inconsistencies in the literature.

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Extent of contribution by PhD candidate (%)	90%

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Name	Nature of Contribution
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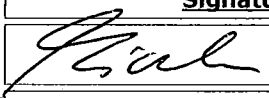
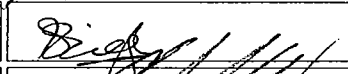
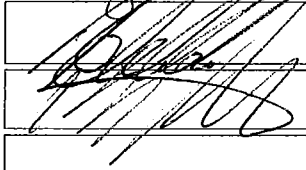
N. S. McKay		31/03/2016
S. S. Singh		30/03/2016
K. E. Waldie		31.03.16
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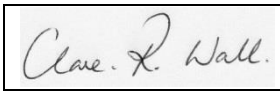
C. Wall		22.03.2016

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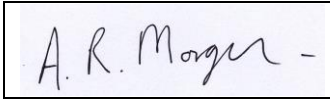
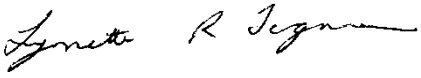
A. R. Morgan		15.03.2016
L. R. Ferguson		16 03 2016

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Chapter 1: General Introduction

1.1 Introduction

In a general population, individuals show noticeable differences in their cognitive abilities. The curiosity this observation generates has inevitably resulted in a search for the foundations of individual differences in cognitive performance that has spanned centuries. Variables internal and external to the individual have been considered, often in isolation and giving rise to the false dichotomy of nature versus nurture. The recent mapping of the human genome has facilitated an explosion of research into the effects of specific genes on cognitive phenotypes, although efforts have tended to yield inconsistent results and effect sizes have typically been small.

This thesis will consider the cognitive effects of variation in the genes coding for brain-derived neurotrophic factor (BDNF) and catechol-*O*-methyltransferase (COMT), two promising candidate genes that have been examined in relation to neuropsychological outcomes. It will be argued that candidate gene research requires clearly defined cognitive outcomes. Forms of memory have different neural substrates and may therefore be affected by different genes. For example, the effects of *BDNF* may be greater for hippocampal-dependent memory than familiarity-based recognition (Lamb, Thompson, McKay, Waldie, & Kirk, 2015). In addition, it is crucial to consider gene-gene, gene-sex, and gene-environment interactions when researching genetic effects on cognition. Particularly relevant for the *COMT* gene is the consideration of hormonal influences and biological sex, which may impact on the relationship between *COMT* genotype and cognitive phenotypes. Individual differences in personality traits such as conscientiousness, which appears to confer neuroprotective effects at higher levels (e.g., Hock et al., 2014; Jackson, Balota, & Head, 2011; Wilson et al., 2015), can also be pertinent to consider; the associated approaches to life

may affect whether a cognitive phenotype becomes manifest. Similarly, gene-environment interactions may reveal otherwise obscured effects on cognition and the antenatal environment in particular may have genotype-specific programming effects.

This initial chapter presents a general introduction to the investigation of genetic effects on cognition. The following four chapters present studies in manuscript style. These studies are then succeeded by a final concluding chapter that discusses the overall findings. The statistical assumption testing for each study is detailed in Appendix A.

1.2 Heritability of cognitive abilities

1.2.1 Cognitive abilities and intelligence

With its linguistic origins in the Latin word 'cognoscere', cognition is the act of knowing, and thus processing, information (Pietropaolo & Crusio, 2011). The term consequently encompasses our abilities for planning, directing of attention, decision-making, learning and memory, as well as the acquisition and processing of language.

Performance on cognitive tasks can differ noticeably from person to person. Spearman (1904) proposed that two key factors contribute to how successful an individual is at performing mental tasks. The first of these is a general cognitive ability factor (Spearman's *g*), which approximates what is typically thought of as intelligence and is represented by the shared variance that is observed between different mental tests. An intelligence quotient (IQ) based on scores from numerous subtests may offer a proxy measurement of this general ability (Wechsler, 2008). The second key factor is a narrow ability that is specific to the particular task. This basic hierarchical model of cognitive ability is still dominant in contemporary research (Bouchard, 1998; Lubinski, 2004; although see Gardner et al., 1996),

with a third level of broad domain skills such as memory, verbal ability and spatial ability now generally thought to lie between them (e.g., Cattell, 1993). While there is some disagreement surrounding whether the overarching *g* factor is required, research tends to support *g* existing at the highest level of the hierarchy rather than being merely a domain-level skill (e.g., Bickley et al., 1995; Carretta & Ree, 1995).

Childhood cognitive abilities have been demonstrated to predict a range of life outcomes such as educational attainment, achieved socioeconomic status, positive psychological development, health and health-related behaviours, quality of life, and longevity (e.g., Batty, Deary, & Macintyre, 2007; Cheng, Green, Wolpert, Deighton, & Furnham, 2014; Deary, Strand, Smith & Fernandes, 2007; Deary et al., 2005; Der, Batty, & Deary, 2009; Johnson, Corley, Starr, & Deary, 2011; Whalley & Deary, 2001). Observations such as these have contributed to widespread interest in elucidating the origins of variation in cognitive abilities.

1.2.2 Twin and adoption studies

Over the last hundred years, twin and adoption studies investigating genetic and environmental contribution to individual differences in cognition have allowed the calculation of heritability estimates for cognitive abilities. In twin studies, the degree of similarity in the cognitive abilities of monozygotic twins is compared with the similarity in dizygotic twins (Plomin & DeFries, 1998). Monozygotic twins have the same genetic material, while dizygotic twins share only about half of their genetic make-up. If genetic factors influence cognitive ability, monozygotic twins should be more similar on measures of cognitive performance than dizygotic twins. Twin studies measuring general cognitive ability, and the more specific domains of verbal ability, spatial ability, and processing speed, have consistently found higher correlations in performance between monozygotic twins than

between dizygotic twins (e.g., Bratko, 1996; McClearn et al., 1997; Pedersen, Plomin, Nesselroade, & McClean, 1992).

The study of monozygotic and dizygotic twins raised in separate households has been argued to be a particularly powerful quasi-experimental design by which genetic and environmental influences on traits may be disentangled (e.g., Bouchard, Lykken, McGue, Segal, & Tellegen, 1990). In adoption studies, the cognitive abilities of genetically related individuals raised in different family environments can be compared, as can the abilities of pairs of non-genetically related individuals raised in the same household. Consequently, the contributions of shared environment and genetics can be examined. In relation to cognitive abilities, adoption studies have produced results similar to those from twin studies and provide complementary information (Plomin & DeFries, 1998). In the Texas Adoption Project, effects of shared family environment on cognitive ability became minor as the adopted individuals moved from childhood into late adolescence (Loehlin, Horn, & Willerman, 1997). Correlations in general cognitive ability between genetically unrelated siblings were substantially lower than those between genetically related siblings. Comparable results were found in the Colorado Adoption Project (Alarcon, Plomin, Fulker, Corley, & DeFries, 1998).

A limitation of twin studies concerns the degree to which environmental factors are the same for monozygotic and dizygotic twin pairs – the controversial "equal environments" assumption (Felson, 2014). As a consequence of their similar physical appearance, the environment and experiences of monozygotic twins may be more similar to those of dizygotic twins (Lewontin, Rose, & Kamin, 1984). Monozygotic twins may also in some cases share a more similar antenatal environmental than dizygotic twins (Phelps et al., 1997; Phillips, 1993; although see van Beijsterveldt et al., 2015). An evaluation of the equal

environments assumption suggests that while this assumption will seldom be strictly valid, the bias resulting from violations is most likely modest (Felson, 2014). Criticisms aimed at adoption studies include the samples not being representative of the general population and possible effects of selective placement (e.g., Kamin & Goldberger, 2002). The restricted range of family environments that children are adopted into could bias estimations of trait heritability (Stoolmiller, 1999). Consequently, there is potential for twin and adoption studies to overestimate influence of genetic factors on individual differences in cognitive abilities.

1.2.3 Heritability estimates for cognitive abilities

A heritability estimate indicates numerically the proportion of variability in a trait that can be attributed to genetic variation (Plomin & DeFries, 1998). The heritability estimate for a given trait reflects the amount of genetic and environmental variability in the particular study. When environmental factors are relatively similar, a greater amount of the variability in cognitive ability would be thus attributed to genetic factors. Therefore heritability estimates may vary from sample to sample and cannot be taken to indicate the extent to which genetics has contributed to the development of an individual. Heritability estimates for general cognitive ability and more specific cognitive abilities can be determined from twin study and adoption study data.

In adults, heritability estimates for general cognitive ability or intelligence have been found to range from .66 to as high as .87 (Finkel, Pedersen, McGue, & McClearn, 1995; Haworth et al., 2009; Luciano et al., 2001; Plomin, Pedersen, Lichtenstein, & McClearn, 1994; Rijsdijk, Vernon, & Boomsma, 2002; Wright et al., 2001). These heritability estimates are suggestive of genetic factors having considerable influence on ability. Specific cognitive abilities tend to show somewhat lower levels of heritability than general cognitive ability (Hermo, Giráldez & Saura, 2011; Pedersen et al., 1992). Heritability estimates for

performance ability (measured using tasks including picture completion, block design and matrix reasoning) in adults have ranged from .35 to .82 (Alarcon et al., 1998; Luciano et al., 2005; Posthuma et al., 2001; Posthuma et al., 2003), although the estimate of .35 came from a sample that also included child participants (Alarcon et al., 1998). More narrow subcomponents of performance ability, such as block design, have produced lower estimates in the range of ~.20 - .50 (Hermo et al., 2014), perhaps due to scores being more heavily under the influence of situational variables and testing anxiety (Paavonen et al., 2010).

Heritability estimates for memory have tended to be smaller than other cognitive abilities [e.g., perceptual speed and verbal ability, which have each been demonstrated to have an average heritability 58% (Pedersen, Plomin, Nesselroade, & McClearn, 1992)] and a particularly wide range of heritability estimates for memory can be found in the literature (Thaper, Petrill, & Thompson, 1994). This may be due to memory measurements differing between studies and many studies only using one or two measures. Unlike many forms of cognition, general memory ability does not show higher heritability than more specific forms of memory (Hermo et al., 2011). Research suggests that some forms of memory are more heritable than others (e.g., Bouchard, Segal, & Lykken, 1990; Finkel, Pedersen, & McGue, 1995; Johansson et al., 1999; Thapar et al., 1994). Genetic factors appear to have a role in episodic memory, with heritability estimates between ~.30 and ~.60 reported (Alarcon et al., 1998; Bouchard et al., 1990; Finkel et al., 1995; Johansson et al., 1999; Swan et al., 1999; Volk et al., 2006). There is some indication that familiarity-based memory tasks (i.e., tasks that entail judging whether stimuli have been previously experienced) may give lower heritability estimates than tasks requiring the binding of contextual information (Thapar et al., 1994) and thus tapping hippocampal-dependent memory (Mitchell, Johnson, Raye, & D'Esposito, 2000). Overall, these studies demonstrates the need to assess memory via a battery of tests rather than a single measure.

Heritability estimates for cognitive abilities do not appear to be stable across development. Haworth and colleagues (2010) demonstrated that the heritability of general cognitive ability shows a linear increase from childhood to young adulthood. This result is supported by a number of studies (e.g., Bergen, Gardner, & Kendler, 2007; Briley & Tucker-Drob, 2013). There is also evidence of comparable increases occurring in the heritability of verbal and, to a lesser extent, non-verbal abilities (Hoekstra, Bartels, & Boomsma, 2007). An age-related increase in the heritability of cognitive abilities is consistent with a genotype-environmental correlation. Over the course of development, we gain increasing ability to seek out and create experiences that are compatible with our genetic inclinations, our genes thus sorting our experiences (Tucker-Drob, Briley, & Harden, 2013). Neurodevelopmental changes in brain structure and function may also contribute to increases in heritability, as these are processes are also under considerable genetic influence (Pietropaolo & Crusio, 2011). For example, twin studies suggest that total brain volume has a heritability in the range of 66–97%; heritability estimates are generally high for frontal lobe (90–95%) and moderate for hippocampal volume (40–69%) (Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007).

The majority of modern researchers acknowledge that both genetic and environmental factors influence our neuroanatomy and cognitive abilities, through a web of complex interactions. High heritability estimates for measurements of cognitive performance should not be interpreted to suggest environment is of little consequence or as placing a ceiling on the potential benefits of social interventions. Rather, the effects of genetics on cognitive abilities are likely to be produced through accrued environmental experiences and may be maximised through exposure to high-quality environmental opportunity (Tucker-Drob et al., 2013).

1.3 Association studies and candidate gene research

Research into the identification of specific genes affecting cognition has been enabled by the sequencing of the human genome. Approximately 20,000 genes are believed to affect central nervous system development, plasticity, and function (Goldberg & Weinberger, 2004; Pietropaolo & Crusio, 2004). Genetic variability in human populations can be characterised by approximately six million single nucleotide polymorphisms (SNPs). Of the common variants, only a minority will be functional and thus alter the expression or behaviour of the proteins that the genes give rise to (Goldberg & Weinberger, 2004). It is not certain how many of these SNPs affect cognitive ability in the general population. One of the main approaches to identifying the genes that underlie human cognition has been the candidate gene association study.

An association study seeks to determine the strength of relationship between the genetic variants of a specific gene and a phenotypic trait of interest. If the relationship is statistically significant, the allele is considered to be associated with that cognitive phenotype. The specific candidate gene should generally be selected on the basis of containing functional polymorphisms and having a potential physiological relationship with the neurobiology of the phenotype (Glatt & Freimer, 2002). The phenotype of interest should be heritable (Goldberg & Weinberger, 2004), as has been shown to be the case for a range of cognitive abilities. Association studies are particularly useful for investigating quantitative traits and can involve samples of related or unrelated participants (Papassotiropoulos & de Quervain, 2011).

Studies of non-human animals have played an important role in informing research on the potential candidate genes involved in human cognition. Candidate genes have been investigated in animal studies through two main approaches (Pietropaolo & Crusio, 2011).

The first of these is comparable to association studies in humans, utilising naturally occurring variation in candidate genes to investigate how behaviour differs between genotypes. The second common approach involves artificial manipulation of the candidate gene. The gene may be rendered inactive, as in knock-out models. Alternatively, extra copies may be inserted, as is the case in transgenic lines. The behaviours of genetically modified animals are compared to those of the wildtype specimen. Consequently the functions and effects of the candidate gene may be deduced, albeit while offering limited information on differences between naturally occurring variants.

Due to the methodological limitations of candidate gene studies, a shift to genome-wide associated (GWA) studies started in around 2005 (Rietveld et al., 2014). GWA studies do not require mechanistic hypotheses and use DNA microarrays to examine associations between a phenotype and potentially over one million SNPs (Plomin, 2013). In cognitive neurogenetics, GWA studies have shown cognitive traits to be massively polygenic, with effects of individual SNPs being considerably smaller than those often reported in candidate gene studies (Plomin, 2013; Plomin, DeFries, Knopik, & Neiderhiser, 2016). Generally, reported candidate gene associations have not been successfully replicated in GWA studies (Manuck & McCaffery, 2014). These discoveries suggest that the inconsistent effects that permeate the candidate gene literature may in part reflect the ubiquity of false positive results emerging from the candidate gene approach; publication bias and underpowered studies are potential contributing factors to false positives in the candidate gene literature (Manuck & McCaffery, 2014).

GWA studies with large samples and stringent corrections for the significance testing of multiple comparisons may better reflect the polygenic nature of complex traits such as cognitive phenotypes. However, GWA studies generally focus on the direct effect of each

SNP on the genotype, without consideration of potential moderating variables (Korte & Farlow, 2013). Gene-environment interactions, for example, which can be readily examined in candidate gene research, may reveal genetic effects that are only manifest in particular environments (e.g., Thompson et al., 2012). Therefore the effects of genes that may only be of practical consequence for certain subgroups can be underestimated by the GWA design, diluted in analyses that collapse across the relevant subgroups (Manuck & McCaffery, 2014). This thesis applies the candidate gene approach, examining variables that may affect whether particular SNPs impact cognitive phenotypes of interest; however, the studies reported are subject to the aforementioned limitations of the candidate gene approach.

1.4 Considerations in candidate gene research on cognition

1.4.1 Effect sizes and replication

As Pietropaolo and Crusio (2011) point out, one-to-one relationships between genetic variants and cognitive phenotypes should not be expected. Traits such as cognitive ability are most likely polygenic, with many genes contributing to the phenotype. Consequently, each individual gene can only be expected to explain a small amount of the variance in cognitive ability and possible gene-gene interactions should be examined. Pleiotropy is also likely, with a single gene impacting on multiple discrete behavioural phenotypes. Researchers often fractionate broader measures of cognitive ability into more specific aspects of cognition in attempt to reduce the genetic complexity (Savitz et al., 2006). Neuropsychological studies inform these divisions. Collapsing over neurologically distinct forms of cognition may reduce sensitivity and potentially mask associations.

The small effect sizes of individual genes may have contributed to the difficulty in replicating candidate gene effects. Replication attempts for previously reported associations between candidate genes and cognitive abilities have tended to be unsuccessful (Chabris et al., 2012). This replication problem appears to be for all complex (polygenic) traits, rather than just behavioural traits (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001; Hirschhorn, Lohmueller, Byrne, & Hirschhorn, 2002). If not adequately controlled for, variables such as age, sex, and education can easily obscure valid associations between genetic variants and cognitive abilities (Goldberg & Weinberger, 2004).

1.4.2 Age- and sex-specific genetic effects

Studies of children and adolescents may produce different results to those of mature individuals. The prefrontal cortex (PFC) continues to develop structurally and functionally through childhood and adolescence (e.g., Blakemore & Choudhury, 2006; Qu, Galvan, Fuligni, Lieberman, & Telzer, 2015). It can be consequently problematic to extrapolate data from child and adolescent samples to adults (Savitz et al., 2006). Certain genes may become active or influential at different stages of neurodevelopment (Tucker-Drob et al., 2013). In a similar manner, results from samples of older adults should be generalised with caution, as the effects of particular genes on cognition and neuroanatomy may be magnified in later life (Papenberg, Lindenberger, & Bäckman, 2015).

Given that the cellular environment in males and females differs as a consequence of differences in hormone levels and gene expression, sex is another easily determined factor that can affect the manifestation of various traits and thus alter relationships between candidate genes and cognitive performance (Weiss, Pan, Abney, & Ober, 2006). These processes may contribute to the population-level sex differences that are observed in some psychological phenotypes (Davies, 2013). Albeit subtle, sex differences in behaviour are

present as early as the neonatal phase of infancy (Boatella-Costa, Costas-Moragas, Botet-Mussons, Fornieles-Deu, & De Caceres-Zurita, 2007). Consideration of potential sex-specific genetic effects is particularly important to consider when investigating the genes of proteins that are thought to interact with sex hormones.

1.4.3 Gene-environment interactions

Environmental conditions may influence whether detrimental effects of a particular gene are manifest, thus producing gene-environment interactions. These interactions have received attention in recent years. An example of a gene-environment interaction can be seen in physical activity, which mitigates the detrimental effects of certain risk alleles on episodic memory (Ferencz et al., 2014). Similarly, environmental enrichment in the forms of high levels of education and intellectual stimulation have been found to attenuate the impact of the apolipoprotein E (*APOE*) e4 allele on dementia occurrence (Wang et al., 2012) and declines in cognitive performance (Vemuri et al., 2014). The protective effects of the *APOE* e2 and e3 alleles on cognitive performance can be strengthened further by following a healthy diet (Whalley et al., 2008). Other genetic variants considered to be risk alleles might require the presence of environmental stressors for detrimental effects to be realised (e.g., Caspi et al., 2003). These such findings in human participants are consistent with earlier animal studies demonstrating that genetically engineered deficits in memory can be amplified by environmental deprivation (Nithianantharajah & Hannan, 2006; Rampon et al., 2000) and lessened by a stimulating environment (Chida, Sudo, Mori, & Kubo, 2006; Dong et al., 2004). Consequently, relevant environmental variables should be taken into account when examining the effects of genes on cognitive ability.

1.4.4 Selection of candidate genes

Appropriate selection of the candidate gene is vital (Goldberg & Weinberger, 2004). Given the importance of the pre-frontal cortex (PFC) for a range of cognitive processes (Benton, 1994), obvious candidate genes may be those expressed in the PFC (Savitz, Solms, & Ramesar, 2006). In particular, genes that affect dopaminergic function are likely to be of consequence for certain cognitive abilities. There is now a strong evidence base connecting the neurotransmitter dopamine to the functioning of the PFC and performance on cognitive tasks (Cools & Robbins, 2004). Similarly, the importance of neurotrophic factors in regulating processes of differentiation, proliferation, and survival for cholinergic, dopaminergic, and serotonergic neurons (Poo, 2001) supports the investigation into genes affecting the expression of neurotrophins.

This thesis focuses on the effects of commonly occurring polymorphisms in the genes coding for brain-derived neurotrophic factor and catechol-*O*-methyltransferase. These are two particularly promising genes that have been implicated in cognitive function.

1.5 Brain-derived neurotrophic factor

Individual differences in how readily the brain modifies itself in response to experiences may contribute to the differences we see in memory abilities (Pascual-Leone et al., 2011). There are a number of variants in the human genome that have been suggested to regulate processes of neuroplasticity (Pearson, Kleim, & Cramer, 2009). Particular attention has been given to the gene coding for brain-derived neurotrophic factor (BDNF). BDNF is secreted in response to environmental stimulation (Lu, 2003) and may be crucial for hippocampal-dependent memory formation. BDNF secretion and localisation is affected by a

frequently occurring SNP in the BDNF gene (Egan et al., 2003). The val^{66}met SNP (rs6265) is associated with differences in brain structure (e.g., Bueller et al., 2006; Chepenik et al., 2009; Frodl et al., 2007; Sanchez et al., 2011) and function (e.g., Hariri et al., 2003), in addition to memory ability (e.g., Egan et al., 2003; Hariri et al., 2003;) and neuroplasticity (e.g., Antal et al., 2010; Cheeran et al., 2008; Fritsch et al., 2010; Thompson et al., 2013). One form of synaptic plasticity that has recently been investigated in connection to the BDNF polymorphism is long-term potentiation (LTP).

LTP induction involves the synchronous activity of pre-synaptic and post-synaptic components (Bliss & Collingridge, 1993; Cooke & Bliss, 2006) and is initiated by post-synaptic calcium incursion (Malenka, Kauer, Zucker & Nicoll, 1988). Consistent with a relationship between LTP and BDNF, BDNF differs from other neurotrophins in that it is released in an activity-dependent manner with secretion being affected by neuronal firing and subsequent levels of calcium ions (Lu, 2003). Accordingly, the process of learning has been found to increase levels of BDNF in rats (Gomez-Pinilla et al., 2007) and monkeys (Tokuyama, Okuno, Hashimoto, Li, & Miyashita, 2000). There are LTP deficits present in BDNF knockout mice which can be reversed through the restoration of BDNF expression (Korte et al., 1996; Patterson et al., 1996). Research on animals has also revealed relationships between LTP and memory performance. Hippocampal-dependent memory is markedly impaired in rats following the inhibition of LTP via N-methyl-D-aspartate (NMDA) receptor antagonism (Morris, Anderson, Lynch & Baudry, 1986) or signalling mechanism disruption (Bozon et al., 2003; Giese et al., 1998). Given these findings, it is likely that BDNF impacts on memory and learning through affecting LTP (Egan et al., 2003; Lamb et al., 2015).

Individuals carrying the met allele of the val66met polymorphism show lower levels of LTP induction (e.g., Thompson et al., 2013), weaker synaptic events (Hariri et al., 2003), and tend to exhibit poorer memory performance (see Koppel & Goldberg, 2009). Effects of vall66met on memory have not been invariably detected (e.g., Hansell et al., 2007; van Wingen et al., 2010). While low statistical power is likely to be hindering replication or leading to false positives in the literature, inconsistencies may also be due in part to differences in the forms of memory being measured and their neural substrates. For example, met homozygosity has been found to be disadvantageous for working memory performance (Gatt et al., 2008) and verbal memory (Schofield et al., 2009). This is consistent with research demonstrating an impact of the met allele on fronto-hippocampal systems normally implicated in memory updating and the processing of selective information relating to stimulus context; on average, met homozygotes display reduced grey matter in the hippocampus and dorsolateral PFC, regions important for memory and attention (Schofield et al., 2009). The met allele may be of less consequence for familiarity-based recognition, a form of memory that appears to be less dependent on the hippocampus and PFC (Aggleton & Brown, 1999; Davidson, Troyer, & Moscovitch, 2006).

1.6 Catechol-*O*-methyltransferase

Another well-described gene is that which codes for catechol-*O*-methyltransferase (COMT). COMT is an enzyme that catabolises catecholamines such as dopamine and norepinephrine. It facilitates a methyl group being transferred from an S-adenosyl-methionine (SAM) donor to the hydroxyl group of a substrate, which may be a catecholamine, catechol oestrogen, or a number of other organic chemicals (Axelrod & Tomchick, 1958; Weinshilboum, Otterness, & Szumlanski, 1999). The COMT enzyme is the

main clearing mechanism for synaptic dopamine in the PFC (Lewis et al., 2001; Sesack, Hawrylak, Matus, Guido, & Levey, 1998), the region where *COMT* is primarily expressed (Gogos et al., 1998; Tunbridge, Burnet, Sodhi, & Harrison, 2004). *COMT* is also abundantly expressed in the hippocampus (Matsumoto et al., 2003). Research on *COMT* knock-out mice has demonstrated increases in dopamine, but not norepinephrine, in the PFC (Gogos et al., 1998). This is consistent with the abundant expression of norepinephrine transporters in the PFC (Moron et al., 2002), while dopamine transporters are scarce in this region (Lewis et al., 2001; Sesack et al., 1998). The finding that COMT mRNA levels are higher in the PFC than in the striatum supports the particular importance of COMT for the neurotransmission of dopamine in the PFC (Matsumoto et al., 2003).

COMT activity is thought to affect the duration of dopamine activity in the synapse, with higher activity terminating the dopamine signal earlier (Egan et al., 2001). COMT activity has been associated with sex hormone levels (Xie et al., 1999) and research on post-mortem human brains has demonstrated sex differences in COMT activity, showing higher COMT activity in men (Chen, Lipska, et al., 2004). COMT activity also changes with age, showing a two-fold increase from infancy to adulthood (Tunbridge et al., 2007). There are a number of commonly occurring SNPs in the *COMT* gene that could be of consequence for the expressed enzyme (Meyer-Lindenberg et al., 2006; Shifman et al., 2002). The most thoroughly studied of these is the *COMT* val^{158}met (rs4680), where the met allele results in lower levels of COMT activity (Chen, Lipska, et al., 2004). Another variant that appears to affect COMT function is the less studied Rs165599 polymorphism (e.g., Bray et al., 2003: Meyer-Lindenberg et al., 2006), which has been associated with psychological disorders (Burdick et al., 2007; Shifman et al., 2002) and memory (Burdick et al., 2007; Chan et al., 2005).

Consistent with the involvement of dopamine in prefrontal function and cognition (Cools & Robbins, 2004), variation in the *COMT* gene has been reported to relate to measures of executive function in both children (e.g., Diamond, Briand, Fossella, & Gehlbach, 2004; Sherman, Hodel, Markant, & Thomas, 2015) and adults (e.g., Barnett, Jones, Robbins, & Müller, 2007; Egan et al., 2003; Goldberg et al., 2003; Wishart et al., 2011). A meta-analysis found evidence of a small effect of the *COMT* val158met polymorphism on IQ performance, although very large samples may be necessary to detect it; *COMT* had no other reliable effects on cognitive outcomes (Barnett, Scoriels, & Munafò, 2008). There is some evidence for gene-environment interactions, with these *COMT* effects on executive function being altered by stress (e.g., Buckert, Kudielka, Reuter, & Fiebach, 2012) and amphetamine administration (Mattay et al., 2003). Amphetamine increases dopamine levels, which could be heightened to the point of detriment in individuals with genetically higher dopaminergic activity.

In terms of memory, the val158met polymorphism has shown a modest yet inconsistent relationship with task performance (e.g., de Frias & Annerbrink, 2004; Dennis et al., 2009; Starr, Fox, Harris, Deary, & Whalley, 2007; Stuart, Summers, Valenzuela, & Vickers, 2014), and may interact with cardiovascular health to affect age-related declines in episodic memory (Persson, Lavebratt, Sundstrom, & Fischer, 2016). Inconsistencies in the literature may have resulted from differences in samples and designs, low statistical power hindering replication or leading to false positives, and potential confounding effects from uncontrolled moderators such as risk factors (Persson et al., 2016) and sex (Papaleo, Sannino, Piras, & Spalletta, 2015).

1.7 Aims and hypotheses

This thesis seeks to further elucidate the specific effects of the *BDNF* and *COMT* genes on cognition, through examining the conditions under which such effects are manifest. Cognitive phenotypes will be clearly defined, with attention to plausible neurobiological routes from gene to phenotype. Variables such as sex, personality traits and environmental stressors may affect whether polymorphisms in the *BDNF* and *COMT* genes are of consequence, and collapsing across such factors may result in neurogenetic effects being obscured; potential gene-sex, gene-trait and gene-environment interactions will thus be explored.

The study presented in Chapter 2 aimed to determine whether the *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms differentially influence performance on recall and recognition tasks (i.e. the Family Pictures I and Faces I subtests of the Wechsler Memory Scale – Third Edition) in a single sample of healthy young adults, and whether the polymorphisms interact to affect performance on either task. Based on the effects of the *BDNF* val^{66}met polymorphism on the hippocampus (Hajek, Kopecek, & Hoschl, 2012; Kambeitz et al., 2012; Molendijk et al., 2012) and the particular role of the hippocampus in recall (Aggleton & Brown, 1999), it was hypothesised that the *BDNF* polymorphism would be associated with recall performance but not familiarity-based recognition. On the recall task, val homozygotes were hypothesised to outperform those with the met allele, thus replicating the results of past research using measures of hippocampal-dependent memory (e.g., Egan et al., 2003; Hariri et al., 2003). As the *COMT* val^{158}met polymorphism appears to be particularly consequential in the PFC (McIntosh et al., 2007), *COMT* genotype was also predicted to affect performance on the recall task, with no effect on recognition. On the recall task, met homozygotes were expected to perform better than individuals with the val allele,

consistent with the effects of the COMT enzyme on relevant brain structures (i.e., PFC and hippocampus; Honea et al., 2009) and replicating de Frias and colleagues (2004). Following from the joint effects of the *BDNF* and *COMT* polymorphisms on cortical plasticity (Witte et al., 2012), the polymorphisms were hypothesised to interact to affect recall performance with the effect of the *BDNF* polymorphism being amplified in those with the *COMT* met allele.

Building upon the results of Chapter 2, Chapter 3 presents a study that aimed to determine whether the *COMT* val^{158}met polymorphism has sex-specific effects on face recognition performance (as assessed using the Faces I subtest) that may be obscured in studies that do not consider gene-sex interactions. This study used the sample from Chapter 2, with further participants added in an effort to bolster statistical power. The *COMT* polymorphism was hypothesised to interact with sex to affect face recognition performance, consistent with research documenting the effects of sex hormones on COMT activity (e.g., Xie et al., 1999) and face recognition performance (Yonker, Eriksson, Nilsson, & Herlitz, 2003). Based on previous research on *COMT*-sex interactions, the met allele was predicted to be beneficial in male participants only.

Conscientiousness is a personality trait that has been demonstrated to have neuroprotective effects in older adults (e.g., Chapman et al., 2012; Hock et al., 2014; Wilson et al., 2015). The study presented in Chapter 4 aimed to determine whether Conscientiousness moderates the effect of the *BDNF* val^{66}met polymorphism on recall performance (as assessed using the Family Pictures I subtest) in young adults. This study used a sample, partially overlapping with that examined in the previous chapters, in which the Revised NEO Personality Inventory (NEO-PI-R) was completed. It was predicted that high levels of Conscientiousness would provide a buffer against the poorer memory performance previously documented (e.g., Lamb et al., 2015) in met allele carriers.

Exposure to antenatal maternal stress has been associated with a range of adverse cognitive outcomes in offspring (Talge et al., 2007) and the *COMT* gene has been linked to different susceptibility to the effects of this environmental stressor (e.g., Thompson et al., 2012). The main aim of the study in Chapter 5 was to determine whether potential effects of antenatal maternal stress on IQ at ages 7 and/or 11 years of age differ between *COMT* Rs165599 or Rs4680 genotypes. It was hypothesised that the cognitive performance of children with the Rs165599 risk allele (G) and/or the Rs4680 met allele would be more affected by maternal stress than that of children without. These effects were predicted to be specific to the programming effects of maternal stress experienced during the antenatal period. This study used longitudinal data from the Auckland Birthweight Collaborative (ABC) study, with child participants administered the Wechsler Intelligence Scale for Children – Third Edition (Wechsler, 1999) at the age of 7 years and the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) at the age of 11 years. Perceived maternal stress was assessed using the Perceived Stress Scale (Cohen & Williamson, 1988).

Chapter 2: Genetic Effects on Recall and Recognition

Preface

Memory is a multifaceted cognitive capacity. One major distinction may be made between episodic recall and familiarity-based recognition. Aggleton and Brown (1999) proposed a model of memory in which the recall of episodic, or episodic-like, information and familiarity-based recognition are carried out by two limbic loops that are largely functionally independent. In this model, recall requires a network of structures that includes the hippocampus and anterior thalamic complex, while familiarity-based recognition is achieved by a second network that includes the perirhinal cortex and mediodorsal thalamus. These hypotheses have received empirical support from a series of animal studies. One key component of episodic recall that can be readily examined in non-human species is memory for spatial information (Aggleton & Brown, 1999). Rats with circumscribed lesions to the hippocampus exhibit significantly impaired spatial memory, indicating the importance of the hippocampus for episodic-like recall (Morris, Garrud, Rawlins, & O'Keefe, 1982). In contrast, lesions to the perirhinal cortex do not affect memory for spatial information in these tasks (Bussey, Muir, & Aggleton, 1999). Lesions to the perirhinal cortex do result in impaired object recognition, as measured by the delayed nonmatching-to-sample (DNMS) test (Meunier, Bachevalier, Mishkin, & Murray, 1993). Hippocampectomies that spare the rhinal cortices do not have any considerable effect on DNMS performance (e.g., Duva et al., 1997; Steele & Rawlins, 1993). Taken together, this research supports a double dissociation in the neural substrates of these two forms of memory.

Human neuroimaging studies have also produced results consistent with Aggleton and Brown's (1999) hypotheses. Hippocampal activation has been demonstrated in numerous functional neuroimaging studies that have used recall-based tasks (e.g., Ryan, Cox, Hayes &

Nadel, 2008; Schacter, Alpert, Savage, Rauch & Albert, 1996; Squire et al., 1992), although perirhinal activity has also been occasionally observed (e.g., Staresina & Davachi, 2006). The hippocampus does not appear to be as heavily involved when performing familiarity-based recognition tasks. A functional magnetic resonance study by Kirk and colleagues (2004) required participants to indicate whether various visual and verbal stimuli presented to them had been encountered in a previous block, a task designed to primarily tax familiarity judgements rather than recall. There was significant activation in the perirhinal cortex and regions of the thalamus such as the mediodorsal nucleus during these familiarity judgements. The hippocampus showed no activation during the judgements. Research by Barense and colleagues (2005) further substantiates these results, with the demonstration of intact recognition performance in amnesiac patients with lesions restricted to the hippocampus, while patients with more extensive medial temporal lobe damage displayed impaired performance.

Forms of memory may have different levels of heritability, with the highest heritability estimates for associative tasks that require the binding of information (Thapar et al., 1994) and are thus dependent on the hippocampus (Mitchell et al., 2000). Recall appears to recruit the hippocampus to a greater extent than familiarity-based recognition (Aggleton & Brown, 1999). Recall and recognition are also likely to be affected by different genes (Nilsson, 2000). While both the *BDNF* val^{66}met (Kambeitz et al., 2012) and *COMT* val^{158}met (e.g., de Frias et al., 2004; Raz et al., 2009) polymorphisms have been associated with memory performance, results have been inconsistent (e.g., Barnett, Scoriels, & Munafo, 2008; Hansell et al., 2007; van Wingen et al., 2010). Conflated phenotypes may contribute to inconsistencies in the literature. The following study examined whether the effects of *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms vary between recall and familiarity-based recognition, two apparently neurologically distinct forms of memory.

The brain-derived neurotrophic factor (BDNF) val^{66}met polymorphism differentially affects performance on subscales of the Wechsler Memory Scale – Third Edition (WMS-III)

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Abstract

Single nucleotide polymorphisms in the brain-derived neurotrophic factor (*BDNF*) gene and the catechol-*O*-methyltransferase (*COMT*) gene influence brain structure and function, as well as cognitive abilities. They are most influential in the hippocampus and prefrontal cortex (PFC), respectively. Recall and recognition are forms of memory proposed to have different neural substrates, with recall having a greater dependence on the PFC and hippocampus. This study aimed to determine whether the *BDNF* val^{66}met or *COMT* val^{158}met polymorphisms differentially affect recall and recognition, and whether these polymorphisms interact. A sample of 100 healthy adults was assessed on recall and familiarity-based recognition using the Faces and Family Pictures subscales of the Wechsler Memory Scale – Third Edition (WMS-III). *COMT* genotype did not affect performance on either task. The *BDNF* polymorphism (i.e. met carriers relative to val homozygotes) was associated with poorer recall ability, while not influencing recognition. Combining subscale scores in memory tests such as the WMS might obscure gene effects. Our results demonstrate the importance of distinguishing between recall and familiarity-based recognition in neurogenetics research.

Keywords

Neurogenetics, BDNF, Memory, Recall, Recognition

2.1 Introduction

Individual differences in the memory ability of healthy individuals are ubiquitous, readily observed both within the laboratory and without. A single nucleotide polymorphism (SNP) found in the gene coding for brain-derived neurotrophic factor (BDNF) has been implicated in variation in mnemonic ability (e.g., Egan et al., 2003; Hariri et al., 2003). Similarly, individual differences in a range of cognitive skills have been attributed partly to a SNP in the gene coding for catechol-*O*-methyltransferase (COMT; e.g., de Frias et al., 2004; Egan et al., 2001). The present study investigated the effects of the *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms on recall and recognition, two neurally dissociable forms of memory.

When researching the potential genetic correlates of memory performance, it is necessary to distinguish between forms of memory. Previous research in this area has often used memory scores that collapse across different forms of memory. However, it is probable that forms of memory are influenced by unique clusters of genes (Nilsson, 2000). One major qualitative division of memory exists between recall and familiarity judgements (Mandler, 1980; Mandler, 2008). Familiarity-based memory, a component of recognition, is the capacity to judge the extent to which a stimulus has previously occurred. This ability does not necessitate the retrieval of specific information concerning the context in which the previous encounters took place (Perfect, Mayes, Downes & Van Eijk, 1996). Recollection, on the other hand, entails the retrieval of precise identifying characteristics of the stimulus, or contextual information such as concepts with which the stimulus was previously associated.

Aggleton and Brown (1999) proposed that these memory functions are the products of two limbic loops that are, to a large extent, functionally independent. The recall of episodic or episodic-like information is achieved by a network of structures involving the hippocampus

and the anterior thalamic complex. Familiarity judgements were proposed to be accomplished by a second network which instead incorporates the perirhinal cortex and the mediodorsal thalamus. Animal studies (e.g., Bussey, Muir & Aggleton, 1999; Duva et al., 1997; Meunier, Bachevalier, Mishkin & Murray, 1993; Morris, Garrud, Rawlins & O'Keefe, 1982; Steele & Rawlins, 1993) and neuroimaging studies of humans (e.g., Kafkas & Montaldi, 2012; Kirk et al., 2004; Ryan, Cox, Hayes & Nadel, 2008; Schacter, Alpert, Savage, Rauch & Albert, 1996; Squire et al., 1992) have provided empirical support for Aggleton and Brown's hypotheses, although there is some recent evidence that the mediodorsal thalamus plays a role in recall (e.g., Pergola et al., 2012; Pergola, Ranft, Mathias & Suchan, 2013).

While most aspects of Aggleton and Brown's (1999) model have received considerable support, one criticism has been that Aggleton and Brown do not fully acknowledge the particular importance of the prefrontal cortex (PFC) in recall (Knowlton, 1999; Parker, 1999). A review by Davidson and colleagues (2006) suggests that the PFC may be more crucial for recall than recognition, although further research into this is necessary. The greater importance of the PFC in recall is consistent with the role this region is thought to play in binding diverse pieces of information together (Fernández & Tendolkar, 2001). From research implicating frontal and medial temporal formations in memory processes, it follows that genes affecting the structure and function of these regions could also influence memory performance.

Part of the neurotrophin family, BDNF is a small, dimeric signalling protein (Lessmann, Gottmann & Malcangio, 2003). BDNF promotes neuronal growth and differentiation whilst the peripheral and central nervous systems develop (Huang & Reichardt, 2003; Poo, 2001). Although the functions of BDNF in the adult brain are less understood (Cunha, Brambilla & Thomas, 2010), BDNF has been found to encourage

neurogenesis in the mature dentate gyrus (Sairanen, Lucas, Ernfors, Castren & Castren, 2005; Scharfman et al., 2005; Thakker-Varia et al., 2014) and striatum (Mohapel, Frielingsdorf, Haggblad, Zachrisson & Brundin, 2005). BDNF also appears to play a vital role in long-term potentiation (LTP; Panja & Bramham, 2014; Poo, 2001), the long-lasting enhancement of synaptic efficacy that is thought to underlie memory and learning (Bliss & Collingridge, 1993; Cooke & Bliss, 2006). Egan and colleagues (2003) proposed that it is through the role of BDNF in LTP that BDNF secretion impacts memory and learning (see Lamb et al., 2014 for a recent review).

The *BDNF* val^{66}met polymorphism produces a non-conservative substitution of a valine with a methionine at codon 66 of this gene (Chen, Patel, et al., 2004; Egan et al., 2003). In a population of European ancestry, 64% of individuals are val homozygotes (val/val), another 3% are met homozygotes (met/met), and the 34% that remain are heterozygotes (val/met; HapMap-CEU). The presence of the met allele has been associated with decreased activity-dependent secretion of BDNF and abnormal intracellular trafficking of the protein (Egan et al., 2003). In accordance with BDNF expression being maximal in the hippocampus (Murer et al., 2001), three meta-analyses have reported that the met allele is associated with lower hippocampal volume (Hajek et al., 2012; Kambeitz et al., 2012; Molendijk et al., 2012). It should however be noted that a later meta-analysis by Harrisberger and colleagues (2014) found no evidence of *BDNF* genotype affecting hippocampal volume, suggesting previous effects may have been overestimated.

In 2003, Hariri and colleagues demonstrated that individuals carrying a met allele show less hippocampal activation during memory encoding and retrieval than val homozygotes, which may reflect impaired synaptic events in the met carriers. A weaker memory trace may be formed, thus accounting for their poorer subsequent performance on

the hippocampal-dependent memory task. While the cumulative literature does suggest that the met allele is detrimental to memory (see Kambeitz et al., 2012 for a meta-analysis), a number of empirical studies have not detected an association between genotype and memory performance (e.g., Hansell et al., 2007; van Wingen et al., 2010). This inconsistency may in part reflect differences in the forms of memory assessed and the extent to which they are dependent on the hippocampus; the *BDNF* polymorphism may be of lesser consequence for forms of memory that recruit the hippocampus to a lesser extent, such as familiarity-based recognition and the conflation of memory-related phenotypes that have different neural substrates may obscure neurogenetic effects.

As with the neurotrophins, neurotransmitters and the proteins that regulate them are integral to neurodevelopment and cognition. The metabolism of released dopamine is catalysed by catechol-*O*-methyltransferase (COMT), with the breakdown of dopamine decreasing levels of this neurotransmitter within the synapse (Egan et al., 2001). Insufficient dopamine has been implicated in deficits across a range of cognitive domains (Nieoullon, 2002), including memory (e.g., Brozoski, Brown, Rosvold & Goldman, 1979; Cai & Arnsten, 1997). Interestingly, excessive dopaminergic activity appears to also be detrimental for the memory functions of the PFC (e.g., Cai & Arnsten, 1997; Zahrt, Taylor, Mathew & Arnsten, 1997). Xu and colleagues (2009) demonstrated that when dopamine is significantly increased in mice, the induction of LTP in the PFC is eroded rather than facilitated.

The activity and thermal stability of the COMT enzyme are influenced by a common SNP located on the coding region of the *COMT* gene (Lachman et al., 1996; Lotta et al., 1995). This val^{158}met polymorphism involves a valine being switched for a methionine. In a European population, 29% are homozygous for the val allele (val/val), 25% are homozygous for the met allele (met/met) and the 46% are heterozygotes (val/met; HapMap-CEU). At body

temperature, the met allele is associated with almost four times more COMT activity than the val allele (Lachman et al., 1996). Met homozygotes would thus be expected to have slower dopamine inactivation than val homozygotes. The alleles appear to be codominant, with heterozygotes displaying an intermediate phenotype (Chen, Lipska, et al., 2004).

COMT genotype has been found to affect grey matter levels in the hippocampus and dorsolateral PFC (Honea et al., 2009). Functional differences have also been observed. In an fMRI study by Egan and colleagues (2001), PFC blood oxygenation level dependent (BOLD) response during a working memory task differed as a function of genotype. The greatest BOLD response was seen in the val homozygotes and may indicate a less efficient system. This differential PFC response has been replicated in a number of later studies (e.g., Jasper, Dideberg, Bours, Maquet, & Collette, 2015; Mattay et al., 2003; Meyer-Lindenberg et al., 2006). As there are few dopamine transporters in the PFC, variation in COMT function could be particularly influential on activity in this region (McIntosh et al., 2007).

COMT genotype has been demonstrated to predict variation in executive function (e.g., Egan et al., 2001; Malhotra et al., 2002; Mitaki et al., 2013) and processing speed (e.g., Bilder et al., 2002), with the met allele typically being associated with superior performance (although a meta-analysis by Barnett et al., 2008 suggests there are no reliable effects of *COMT* genotype on aspects of cognition other than IQ). A number of studies have reported met homozygotes to have an advantage on memory tasks when compared to val carriers (e.g., de Frias et al., 2004; Enoch, Waheed, Harris, Albaugh & Goldman, 2009; Raz et al., 2009). De Frias and colleagues (2004) found that when episodic memory was broken down into its elements of recall and recognition, a significant difference between genotypes was only present for the recall component. This differential effect demonstrates that the polymorphism

could have some degree of memory specificity, possibly driven by the relative involvement of the PFC.

As conflated phenotypes may have contributed to inconsistencies in the literature, the present study explored whether the effects of *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms vary between recall and familiarity-based recognition, two apparently neurologically distinct forms of memory. The present study aimed to examine both recall and recognition performance in the same group of participants, to determine (1) whether the *BDNF* val^{66}met polymorphism differentially influences performance on recall and recognition tasks; (2) whether the *COMT* val^{158}met polymorphism differentially influences performance on recall and recognition tasks; and (3) whether the *BDNF* val^{66}met and *COMT* val^{158}met polymorphism interact to influence either recall or recognition performance. Based on the particular influence of the *BDNF* val^{66}met polymorphism on the hippocampus and the specific dependency of recall on the hippocampus, it was hypothesised that the *BDNF* polymorphism would influence recall but not familiarity-based recognition. On the recall task, val homozygotes were expected to outperform those with the met allele, thus replicating the results of past research on hippocampal-dependent memory (e.g., Egan et al., 2003; Hariri et al., 2003). As the influence of the *COMT* val^{158}met polymorphism appears to be highest in the PFC, *COMT* genotype was also predicted to solely affect performance on the recall task. On this task, met homozygotes were expected to perform better than individuals with the val allele, replicating de Frias and colleagues (2004).

BDNF plays a pivotal role in the development of dopaminergic-related systems (Zhou, Bradford & Stern, 1994), while COMT levels affect the structure of frontal and limbic regions (e.g., Honea et al., 2009). Furthermore, BDNF (Poo, 2001) and COMT (Jacobsen, Eriksen, Pedersen & Gjerstad, 2010) both influence forms of LTP and a study by Witte and

colleagues (2012) has noted that the *BDNF* and *COMT* polymorphisms interact to impact on cortical plasticity. A *BDNF* and *COMT* interaction has also been recently reported for immediate recall in older adults (Stuart, Summers, Valenzuela, & Vickers, 2014). Consequently, it was hypothesised that an interaction between the *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms might be found for recall performance. Following from the results of Witte and colleagues (2012), it was hypothesised that the detrimental effect of the *BDNF* met allele on recall performance would be greatest in participants with the *COMT* met allele.

2.2 Material and methods

2.2.1 Participants

A sample of 100 healthy university students aged between 18 and 42 years (M = 23.3, SD = 4.0) participated in this study. Of these participants, 64 were female. Self-reported ethnicities were European or Pakeha (70%), Asian (21%), Indian (6%), Middle Eastern (1%) and Mixed (2%). Participants had either normal or corrected-to-normal vision. All participants gave their informed consent for inclusion in this study and the University of Auckland Human Subjects Ethics Committee approved all study procedures.

2.2.2 Genotyping

2.2.2.1 DNA collection.

Participants were asked to give a small blood sample or saliva sample. Blood sample collection was performed with sterile procedures. Saliva samples were collected using Oragene-DNA Self Collection kits in a manner consistent with the manufacturer's instructions.

2.2.2.2 DNA extraction.

DNA was extracted from the blood samples following the method outlined by Miller, Dykes and Polesky (1988) and from the saliva samples following the method given by Nishita and colleagues (2009). All resultant DNA samples were resuspended in Tris-EDTA buffer and were quantified used Nanodrop ND-1000 1-position spectrophotometer (Thermo Scientific).

2.2.2.3 DNA amplification.

The DNA samples were all diluted to 50 ng/μL. A modified version of the method described by Erickson and colleagues (2008) was used for the DNA amplification. Amplification was carried out on the 113 bp polymorphic *BDNF* fragment, using the primers BDNF-F 5'-GAG GCT TGC CAT CAT TGG CT-3' and BDNF-R 5'-CGT GTA CAA GTC TGC GTC CT-3'. Amplification of the 176 bp polymorphic *COMT* fragment used the primers COMT-F 5'-TCA CCA TCG AGA TCA ACC CC-3' and COMT-R 5'-GAA CGT GGT GTG AAC ACC TG-3'. Polymerase chain reaction (PCR) was conducted using 10X Taq buffer (2.5L μL), Taq polymerase (0.125 μL), dNTPs (5 nmol), primers (10 pmol each), Q solution (5 μL) and DNA (100 ng) made up to 25 μL with dH_2O. The PCR conditions consisted of denaturation at 95 ◌̊C for 15 min, 30 cycles on a ThermoCycler (involving denaturation at 94 ◌̊C for 30 s, annealing at 60 ◌̊C for 30 s, and extension at 72 ◌̊C for 30 s) and a final extension at 72 ◌̊C.

2.2.2.4 Enzyme digestion.

For *BDNF*, PCR product (6.5 μL) was incubated with Pm1l at 37 ◌̊C overnight. For *COMT*, PCR product (8 μL) was incubated with N1aIII at 37 ◌̊C for 1 hr. The digestion products were analysed using a high-resolution agarose gel (4%) with a Quick Load 100 bp

ladder (BioLabs) and a GelPilot Loading Dye (QIAGEN). After immersion in an ethidium bromide solution for 10 min, DNA was visualized under ultraviolet light.

2.2.2.5 Genotyping.

For *BDNF*, enzyme digestion resulted in a 113 bp fragment for the met^{66} allele, which was cut into 78 bp and 35 bp fragments for the val^{66} allele. For *COMT*, digestion resulted in bands of 82, 54 and 41 bp for the val^{158} allele and the 82 bp fragment was cut into 64 and 18 bp fragments for the met^{158} allele. This was as described by Erickson and colleagues (2008).

2.2.3 Memory measurements

Familiarity and recall performance were assessed using two subtests from the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). These subtests were the Faces and Family pictures tasks, each of which tap into visual memory. In the Faces subtest, participants were presented with 24 images of faces that they were requested to remember. The faces were presented serially for 2 s each. Immediately after being presented with this list, participants were shown 48 faces, half of which they had just seen and the rest of which were novel. For each of these, participants were required to make a judgement as to whether or not they had previously been shown it. Raw Faces scores were converted into percentage correct for each participant.

In the Family Pictures task, participants were first introduced to images of a fictional family consisting of seven members. They were then presented with four scenes in turn, shown for 10 s each. Within each of these scenes, up to four members of the fictional family appear engaged in various activities in unique spatial locations. Immediately subsequent to the viewing of these, participants were asked set questions that assessed their memory of the scenes. These questions related to the activities and locations of each character. Unlike the Faces subtest, the Family Pictures subtest necessitates recall, with contextualised details of

the scenes being retrieved from memory. Raw Family Pictures scores were converted into percentage correct for each participant.

2.2.4 Data analysis

2.2.4.1 Data preparation.

Observed *BDNF* genotypes did not differ significantly from those predicted by Hardy Weinberg equilibrium ($\chi^2 = 0.849$, $p > .05$). Of the 100 participants, 53 (53.0%) were val (G) homozygotes, 10 (10.0%) were met (A) homozygotes and 37 (37.0%) were heterozygotes (val/met; G/A). *BDNF* genotypes were dichotomised into val homozygotes and met allele carriers for analysis. While research would ideally distinguish between the *BDNF* val/met and met/met genotypes, this is often not practical due to the rarity of met homozygotes and low sample sizes. Consequently, numerous previous studies have combined heterozygotes and met homozygotes in this manner (e.g., Erickson et al., 2008; Pezawas et al., 2004), still detecting significant differences.

For similar reasons, *COMT* genotypes were dichotomised into met homozygotes and val allele carriers. A number of prior cognitive studies have found only the *COMT* met homozygotes to significantly differ from the other genotypes, supporting the decision of grouping the heterozygotes and val homozygotes together (e.g., Malhotra et al., 2002; Tsai et al., 2003). *COMT* genotypes in the present study did not differ significantly from those predicted by Hardy Weinberg equilibrium ($\chi^2 = 0.998$, $p > .05$). Of the 100 participants, 27 (27.0%) were val (G) homozygotes, 28 (28.0%) were met (A) homozygotes and 45 (45.0%) were heterozygotes (val/met; G/A).

2.2.4.2 Statistical analyses.

A MANOVA was conducted on the Family Pictures (recall) scores and Faces (recognition) scores, with *BDNF* genotype (val/val and met allele) and *COMT* genotype (val allele and met/met) as the between-subjects independent variables. Mean recall and recognition scores for *BDNF* and *COMT* genotypes are shown in Table 2.1.

Mean recall and recognition scores for *BDNF* and *COMT* genotype combinations (no genotypes combined) are shown in Table B1.1 and Table B1.2. Additional MANOVAs were conducted on the Family Pictures (recall) scores and Faces (recognition) scores, with *BDNF* genotype at two levels (val/val and met allele) and *COMT* genotype at three levels (val/val, val/met and met/met) as the between-subjects independent variables (Table B1.3), and with *BDNF* genotype at three levels (val/val, val/met and met/met) and *COMT* genotype at three levels (val/val, val/met and met/met) as the between-subjects independent variables (Table B1.4).

2.3 Results

Results of the MANOVA are shown in Table 2.2. The MANOVA revealed a significant main effect of *BDNF* genotype on recall performance ($F_{(1,96)} = 6.204$, $p = .014$). This main effect is shown in Fig. 2.1. On average, *BDNF* val homozygotes ($\underline{M} = 79.3$, $SE = 2.10$) attained significantly higher recall scores than met allele carriers ($\underline{M} = 72.0$, $SE = 2.06$).

A two-way interaction between *BDNF* and *COMT* genotype on recall scores was approaching significance ($F_{(1,96)} = 3.864$, $p = .052$). It should be noted that neither this interaction trend nor the main effect of *BDNF* on recall appear to have been driven by influential outliers. Data screening results were not consistent with the presence of influential

Table 2.1

Mean Recall and Recognition Scores for BDNF and COMT Genotypes

Form of Memory	*BDNF*	*COMT*	Mean	Std. Error	*N*
Recall	Val/Val	Val allele	76.8	2.08	40
		Met/Met	81.8	3.65	13
		Total	79.3	2.10	53
	Met allele	Val allele	75.3	2.32	32
		Met/Met	68.8	3.40	15
		Total	72.0	2.06	47
	Total	Val allele	76.1	1.56	72
		Met/Met	75.3	2.49	28
		Total	75.8	1.34	100
Recognition	Val/Val	Val allele	79.1	1.71	40
		Met/Met	81.1	3.01	13
		Total	80.1	1.73	53
	Met allele	Val allele	78.8	1.92	32
		Met/Met	82.6	2.80	15
		Total	80.7	1.70	47
	Total	Val allele	78.9	1.29	72
		Met/Met	81.9	2.05	28
		Total	79.8	1.08	100

Table 2.2

MANOVA for Recall (Family Pictures) and Recognition (Faces) Scores with BDNF Genotype and COMT Genotype as the Between-Subjects Variables

Source		*F*	df	*p*
BDNF Genotype	Recall	6.204*	1	.014
	Recognition	.068	1	.795
COMT Genotype	Recall	.068	1	.795
	Recognition	1.477	1	.227
BDNF*COMT	Recall	3.864	1	.052
	Recognition	.143	1	.706
Error			96	

*$p < .05$

outliers and Shapiro-Wilk tests indicate recall scores were sufficiently normally distributed for each *BDNF* and *COMT* genotype combination ($p > .05$).

No other effects or interactions were significant for recall or recognition.

In the additional analysis in which COMT was tested at three levels, the main effect of *BDNF* on recall approached significance while the *BDNF* and *COMT* interaction term did not, while no effects were significant in the analysis with both *COMT* and *BDNF* tested at three levels (Table B1.3 and B1.4); however, cell sizes and statistical power were reduced in these analyses (Tables B1.1 and B1.2).

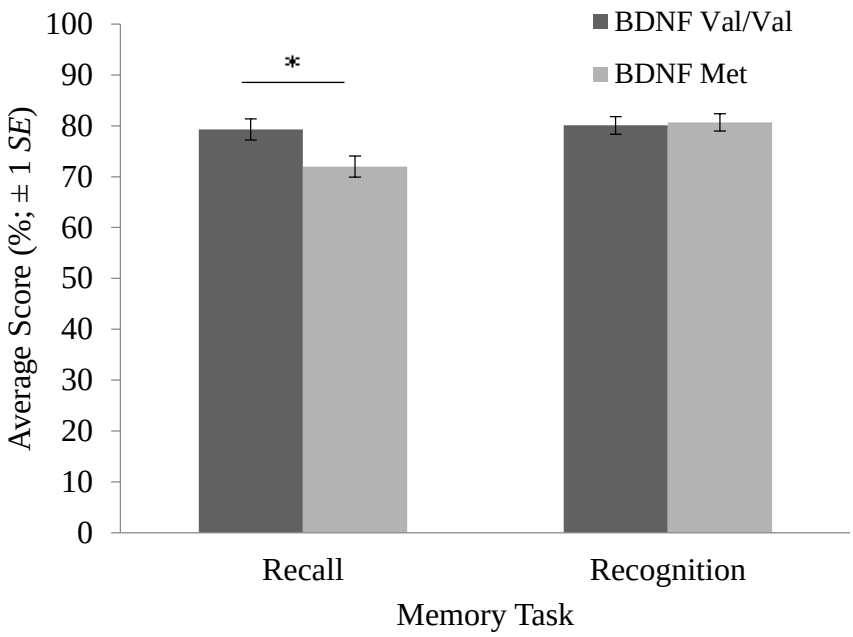

Fig. 2.1. Recall and recognition scores for participants with the *BDNF* val/val genotype and participants with at least one copy of the *BDNF* met allele.

The error bars are based on ± one standard error.

*$p < .05$

2.4 Discussion

Support was found for the hypothesis that the *BDNF* val^{66}met polymorphism would differentially affect recall and familiarity-based recognition. As predicted, there was a main effect of *BDNF* genotype for recall scores, with val homozygotes significantly outperforming those with a copy of the met allele. In contrast, there was no effect of *BDNF* genotype on recognition scores. The superior performance of val homozygotes on the recall task replicates previous studies that have assessed hippocampal-dependent memory (e.g., Egan et al., 2003; Hariri et al., 2003). Similarly, the lack of effect on familiarity-based recognition reproduces the null effects reported by van Wingen and colleagues (2010). The differential effect of the *BDNF* polymorphism on recall and recognition suggests that *BDNF* is less influential on

extra-hippocampal structures and processes than it is on those of the hippocampus. This interpretation is consistent with research showing the anatomical and physiological effects of BDNF to be particularly salient in the hippocampus (e.g., Hofer et al., 1990), as well as Hariri and colleagues' (2003) demonstration of *BDNF* genotype having a hippocampal-specific impact on activation levels. Consequently, the results from the present study may help explain some of the inconsistencies in the existing literature (see Mandelman & Grigorenko, 2012, and Kambeitz et al., 2012 for recent meta-analyses), in that *BDNF* is unlikely to be implicated in memory in studies where memory is assessed solely on familiarity judgements.

The differential effect on recall and recognition found in the present study has implications for theories of memory, particularly that of Aggleton and Brown (1999). Aggleton and Brown's distinction between recall and familiarity-based recognition has been criticised on the grounds that the importance of recollection in familiarity-based recognition is widely acknowledged, with the overlap between recall and familiarity-based recognition rendering a neural dissociation between these forms of memory invalid (e.g., Mayes, van Eijk, Gooding, Isaac & Holdstock, 1999). The results of the present study suggest that the difference between recall and recognition is sufficient to have practical consequences for research, as well as possible clinical applications. A distinction between recall and familiarity-based recognition should be considered by researchers investigating the genetics and neural processes involved in memory.

The hypothesis that the *COMT* val^{158}met genotype would differentially affect recall and recognition performance was not supported in the present study. *COMT* genotype affected neither recall nor recognition. This is inconsistent with previous studies that have found *COMT* genotype to have consequences for memory. Research by de Frias and colleagues (2004) reported that the *COMT* met allele was beneficial for recall performance,

while not affecting recognition. The failure of the present study to replicate this result may be a consequence of differences between the participant samples. De Frias and colleagues' research sample consisted of older participants, whereas the present study examined the performance of young adults. Furthermore, de Frias and colleagues' study only involved male participants. Research indicates that the impacts of the *COMT* polymorphism on cognition can vary with age (e.g., Nagel et al., 2008), and that sex differences might be present (e.g., O'Hara et al., 2006). It should also be noted that meta-analyses (e.g., Barnett et al., 2008) suggest the effects of *COMT* on memory and other forms of cognition may not be as large as initially thought. Furthermore, other genetic variants affecting the dopaminergic system, such as the dopamine receptor D1 (*DRD1*) and D2 (*DRD2*) SNPs, should ideally be included in studies looking at the effects of *COMT*. When studied in isolation the effects of a single polymorphism on memory may be obscured (Gosso et al., 2008).

While we found a trend towards *BDNF* and *COMT* genotypes interacting to affect recall, this did not reach significance. It is possible that our study lacked the statistical power necessary to detect an interaction effect, due to having insufficient participants with certain *BDNF* and *COMT* genotypic combinations. While there is pre-existing evidence that *BDNF* genotypes influence levels of LTP induction (Thompson et al., 2013) and may interact with *COMT* genotypes in doing so (Witte et al., 2012), an effect on this brain-based phenotype may not necessarily result in a robust cognitive phenotype. While Stuart and colleagues (2014) did detect a significant interaction between *BDNF* and *COMT* on immediate auditory recall in older adults, their sample was larger and the effect size modest. Neurophysiological measures may be a more immediate reflection of the neurobiological effects of genes than more distal behavioural measures, as performance on behavioural tasks can be swayed by a multitude of additional factors including motivation, strategy use and attitude to assessment (Goldberg & Weinberger, 2004). Consistent with this, Kambeitz and colleagues (2012) found

that the *BDNF* polymorphism has a weaker effect on memory performance than it does on hippocampal physiology.

Further studies replicating aspects of the present study would be constructive. The present study had several limitations, some of which were consequences of its small sample size. Due to having a limited number of participants of each genotype for each polymorphism, some genotypes were combined. As a result, this study was not capable of investigating the dosage effects that previous studies have reported to be evident across the three genotypes that result from each polymorphism (e.g., Beste, Baune, Domschke, Falkenstein & Konrad, 2010; Egan et al., 2001; Wang et al., 2014). A study with a larger sample size would allow research into additional variables that could potentially influence the effects of these polymorphisms on memory. These variables include age, gender and general intelligence, as well as further genes (e.g., *DRD1* and *DRD2*). Furthermore, the participant sample in the present study was of mixed ethnicity and there is evidence to suggest the effects of the *BDNF* and *COMT* genes may vary between ethnic groups (Shimizu, Hashimoto, & Iyo, 2004; Wang, Ma, Yuan, Su, & Li, 2016).

There are also limitations associated with the use of the Faces and Family Pictures tasks from the WMS-III, tasks which have not been included in a more recent edition of the scale (WMS-IV; Wechsler, 2009) due in part to issues associated with their scoring systems (Pearson, 2009). In the present study, the Faces and Family Pictures tasks were scored according to the WMS-III Administration and Scoring Manual (Wechsler, 1997). Many of our participants lost marks on the Family Pictures task due to misidentifying characters with similar appearances. As a consequence of these errors, they could not receive marks for any correct recall of the location and activity associated with that misidentified character. Therefore visual discrimination and recognition abilities also played a role in determining the

scores participants received in the Family Pictures task, rather than it being a pure test of recalled associations. This is less than ideal and future research may look to replicate the present result with a more valid recall measure.

The present study contributes to our understanding of the genetic influences on normal memory variation in healthy young adults. It replicates and builds upon previous findings in demonstrating that the *BDNF* val allele benefits recall performance while not influencing familiarity-based recognition performance. The role of *BDNF* in the structure and function of the hippocampus in particular is consistent with the effect of the *BDNF* polymorphism being specific to hippocampal-dependent forms of memory such as recall. This differential effect on recall and recognition substantiates the legitimacy and desirability of distinguishing between these forms of memory when investigating the genetic underpinnings of memory. Combining subscale scores such as is usually done in the WMS will likely obscure the effects of the *BDNF* polymorphism. Sensitivity may be lost when collapsing across different cognitive phenotypes, contributing to inconsistencies in the literature.

Chapter 3: *COMT*-Sex Interaction Affects Recognition

Preface

Sex is an influential variable in neuroscience (Cahill, 2006). There are sexual dimorphisms in structural and functional parameters of the brain (e.g., De Vries, 2004; Ingalhalikar et al., 2013; Preece & Cairns, 2003; Sacher, Neumann, Okon-Singer, Gotowiec, & Villringer, 2013) which are likely to be primarily due to differences in sex hormones (Kelly, Ostrowski, & Wilson, 1999; Rubinow & Schmidt, 1996). Sex hormones such as oestrogen have been demonstrated to impact the expression of various genes linked to brain function (e.g., Bethea, Kohama, Reddy, & Urbanski, 2016; Vamvakopoulos & Chrousos, 1993). Oestrogen affects the dopaminergic system (Becker, 1990) and levels of COMT activity (Xie et al., 1999), while the COMT enzyme is in turn important for the methylation of catechol oestrogens (Weinshilboum et al., 1999). Interactions between the COMT enzyme and oestrogens could contribute to the presence of sex differences in cognitive and behavioural phenotypes (Davies, 2013). These interactions could be affected further by variation in the *COMT* gene. It is thus important to consider sex as a moderating variable in the relationship between *COMT* and cognitive outcomes.

The following study sought to determine whether there is a sex-specific effect of the *COMT* val158met polymorphism on face recognition that was obscured in the first study. Data were collected from further participants to improve statistical power, thus allowing the hypothesised gene-sex interaction to be tested.

Catechol-*O*-methyltransferase val^{158}met polymorphism interacts with sex to affect face recognition ability

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Abstract

The catechol-*O*-methyltransferase (*COMT*) val158met polymorphism affects the breakdown of synaptic dopamine. Consequently, this polymorphism has been associated with a variety of neurophysiological and behavioural outcomes. Some of the effects have been found to be sex-specific and it appears oestrogen may act to down-regulate the activity of the COMT enzyme. The dopaminergic system has been implicated in face recognition, a form of cognition for which a female advantage has typically been reported. This study aimed to investigate potential joint effects of sex and *COMT* genotype on face recognition. A sample of 142 university students was genotyped and assessed using the Faces I subtest of the Wechsler Memory Scale – Third Edition (WMS-III). A significant two-way interaction between sex and *COMT* genotype on face recognition performance was found. Of the male participants, *COMT* val homozygotes and heterozygotes had significantly lower scores than met homozygotes. Scores did not differ between genotypes for female participants. While male val homozygotes had significantly lower scores than female val homozygotes, no sex differences were observed in the heterozygotes and met homozygotes. This study contributes to the accumulating literature documenting sex-specific effects of the *COMT* polymorphism by demonstrating a *COMT*-sex interaction for face recognition, and is consistent with a role for dopamine in face recognition.

Keywords

Neurogenetics, COMT, Recognition, Gene-Sex Interaction, Memory

3.1 Introduction

Faces are a ubiquitous feature of our social environment. Generally, research has documented a female advantage for remembering previously encountered faces (Herlitz & Lovén, 2013). The dopaminergic system has been implicated in face recognition (e.g., Rypma et al., 2015) and dopamine availability in the mammalian central nervous system is affected by the catechol-*O*-methyltransferase (COMT) enzyme (Egan et al., 2001). Activity of the COMT enzyme is affected by variation in the gene coding for the COMT, which includes the *COMT* val^{158}met polymorphism (Chen, Lipska, et al., 2004). COMT activity is also regulated by oestrogen (e.g., Jiang, Xie, Ramsden & Ho, 2003), and certain effects of the *COMT* polymorphism on cognition appear to be sex-specific (e.g., Barnett et al., 2007; Gurvich & Rossell, 2015; Soeiro-De-Souza et al., 2013). This study investigated the potential sex-specific effects of the *COMT* val^{158}met polymorphism on memory for faces in young adults.

Sex differences are commonly reported for a range of cognitive functions and their underlying neural substrates. Numerous studies involving face recognition tasks have reported that women recognise significantly more faces than men (e.g., Guillem & Mograss, 2005; O'Toole et al., 1998; Rehnman & Herlitz, 2007). Although sex differences have not been invariably found (e.g., Haut & Barch, 2006; van Wingen et al., 2010), a recent meta-analysis by Herlitz and Lovén (2013) noted a significant overall effect of sex on memory for faces. This female advantage was present at similar magnitudes in children, adolescents and adults (Herlitz & Lovén, 2013). At the neuroanatomical level, girls and women show larger fusiform face areas (FFAs) than boys and men (e.g., Golarai, Liberman, Yoon & Grill-Spector, 2009). The FFA is a face-specific region of the fusiform gyrus, an integral component of the face processing network (Gobbini & Haxby, 2007; Kanwisher, McDermott, & Chun, 1997; Sergent & Signoret, 1992). Larger FFAs have in turn been linked to higher

levels of face recognition performance (e.g., Furl, Garrido, Dolan, Driver, & Duchaine, 2011; Golarai et al., 2009).

The biopsychosocial model of sex differences in cognition describes biological and environmental factors as being intertwined, interacting with each other to affect cognitive phenotypes (Halpern, 2012). Early perceptual experiences have been suggested to contribute to females developing a higher level of expertise in recognising faces (Herlitz & Lovén, 2013). Sex hormones may also play a role in memory-related sex differences, with oestrogen affecting brain regions involved in learning and memory (Pompili, Arnone, & Gasbarri, 2012) and enhancing the release of striatal dopamine (Becker, 1990; Becker & Rudick, 1999). In young women, a single dose of progesterone decreases activity in the fusiform gyrus and amygdala during the encoding of faces, resulting in poorer subsequent face recognition (van Wingen et al., 2007). Estradiol is positively associated with face recognition performance in females while no association is seen in males (Yonker et al., 2003).

The dopaminergic system appears to influence fusiform gyrus activity and face recognition performance. Kim and colleagues (2010) found that participants given the dopamine precursor L-dihydroxypheylalanine (L-dopa) showed greater activation in the bilateral fusiform gyrus compared to participants assigned a placebo. Recently, Rypma and colleagues (2015) reported that local dopamine availability, as assessed using dopamine D1 binding potential, predicts neural activity in the fusiform gyrus during a face recognition task. A high blood-oxygen-level-dependent (BOLD) response relative to dopamine availability supported higher face recognition performance. Similarly, dopamine has been consistently implicated in the reward system (Taber, Black, Porrino, & Hurley, 2012) and faces can be rewarding stimuli (e.g., Stavropoulos & Carver, 2014). Reward associated with viewing faces may affect how memorable those faces are (Marzi & Viggiano, 2010).

The COMT enzyme metabolises synaptic catecholamines, accounting for over 60% of the degradation of dopamine in the mammalian frontal cortex (Karoum, Chrapusta, & Egan, 1994). The gene coding for COMT contains a functional single nucleotide polymorphism (SNP) that affects the thermal stability and activity of the enzyme (Lachman et al., 1996; Lotta et al., 1995). The *COMT* val158met SNP involves a valine (val) being substituted for a methionine (met). Studies suggest the met allele decreases COMT activity by somewhere between 30% (Chen, Lipska, et al., 2004) and 67 - 75% (Lachman et al., 1996). Consequently, dopamine presumably remains active in the synapse for a longer duration, leading to enhanced dopamine signalling (Weinberger et al., 2001). The *COMT* alleles are co-dominant, and heterozygotes typically display an intermediate phenotype (Chen, Lipska, et al., 2004; Lachman et al., 1996). *COMT* heterozygotes (val/met) make up 46% of a European population, while 29% are val homozygotes (val/val) and 25% are met homozygotes (met/met; HapMap-CEU).

Maintenance of both *COMT* alleles in the population may be explained using the warrior/worrier dichotomy proposed by Goldman, Oroszi, and Ducci (2005), in which the *COMT* val allele is associated with both stress resistance and poorer cognitive performance, while the evolutionarily more recent met allele confers cognitive advantages but also affective vulnerability. Research indicates the met allele is associated with better performance on tasks tapping working memory (Aguilera et al., 2008; Goldberg et al., 2003), processing speed (Bilder et al., 2002), and executive functions (Egan et al., 2001; Malhotra et al., 2002; Rosa et al., 2004). Despite these positive reports, studies on COMT genotype and cognition have produced inconsistent results. A meta-analysis of the effects of *COMT* genotype on a range of cognitive phenotypes reported no associations between *COMT* and any phenotypes other than IQ (Barnett, Scoriels, & Munafò, 2008). Barnett and colleagues (2008) suggest that early promising results and a publication bias may have contributed to potentially

unwarranted enthusiasm concerning the effects of *COMT* on cognition. Between-study heterogeneity indicates that relationships between COMT and cognition may vary between populations, or as a consequence of a number of other population-independent variables (Barnett et al., 2008).

Sex-specific effects of the *COMT* polymorphism on cognition could contribute to inconsistencies in the literature, as these effects may be obscured when sex is not considered in the analysis. There is accumulating evidence of *COMT* genotype-sex interactions on a range of phenotypes, including psychiatric disorders (Harrison & Tunbridge, 2008), personality traits (Chen et al., 2011), and forms of cognition such as verbal ability and memory (O'Hara et al., 2006; Soeiro-De-Souza et al., 2013). There is some indication that the impact of *COMT* genotype on cognition may be stronger in males than in females (Barnett et al., 2007; Harrison & Tunbridge, 2008). An inverted "U"- shaped relationship is thought to exist between dopamine and cognitive performance, with cognition being impaired by suboptimal and supraoptimal dopamine levels (Mattay et al., 2003; Vijayraghavan et al., 2007). Factors such as genotype and sex may interact to influence an individual's baseline position on this hypothetical curve (O'Hara et al., 2006).

Interactions between *COMT* genotype and sex may be at least in part due to regulatory effects of oestrogen on dopaminergic transmission and COMT activity. Oestrogen appears to facilitate the release and synthesis of dopamine (Becker, 1990, 2000; Pasqualini et al., 1995; Xiao & Becker, 1994) and may thus contribute to sex differences documented for cognitive phenotypes. Oestrogen has been reported to decrease COMT mRNA levels and activity (Cohn & Axelrod, 1971; Jiang et al., 2003; Xie et al., 1999). Consistent with these down-regulation effects of oestrogen on COMT, women with particularly high levels of oestrogen (due to being in the third trimester of pregnancy or taking an oral contraceptive)

show lower levels of COMT activity than other women (Briggs & Briggs, 1973). Furthermore, Chen, Lipska and colleagues (2004) found that prefrontal COMT activity was around 17% higher for males than for females. This finding was independent of *COMT* val158met genotype. These higher levels of activity occur despite COMT protein and mRNA levels not differing between males and females (Bray et al., 2003; Chen, Lipska, et al., 2004; Tunbridge, Burnet, Sodhi, & Harrison, 2004).

The present study builds upon that previously reported by Lamb and colleagues (2015), in which *COMT* val^{158}met genotype did not affect face recognition performance in a smaller sample of young adults. The aim of the present study was to determine whether the *COMT* val^{158}met polymorphism has sex-specific effects on face recognition performance that may be obscured in studies that do not consider genotype-sex interactions. Due to the effects of oestrogen on COMT activity and face recognition performance, as well as previously documented *COMT* genotype-sex interactions, the *COMT* polymorphism was hypothesised to interact with sex to affect face recognition performance; the met allele was only predicted to be beneficial in male participants. We also predicted a significant main effect of sex on face recognition, replicating past studies.

3.2 Material and methods

3.2.1 Participants

A sample of 142 university students aged between 18 and 42 years (M = 22.7, SD = 3.8) participated in the present study. Of these participants, 90 (63.4%) were female and 100 (70.4%) were participants from the study previously published by Lamb and colleagues (2015). Self-reported ethnicities were European or Pakeha (63%), Asian (21%), Indian

(11%), Middle Eastern (1%) and Mixed (4%). All participants had either normal or corrected-to-normal vision. They had no learning disabilities and gave their informed consent for inclusion in this study.

3.2.2 Genotyping

3.2.2.1 DNA collection.

Participants were requested to provide a small blood or saliva sample. Blood collection occurred under sterile conditions. Saliva samples were collected using Oragene-DNA Self Collection kits following the instructions of the manufacturer.

3.2.2.2 DNA extraction.

DNA extraction from the blood samples followed the method given by Miller, Dykes and Polesky (1988) , while extraction from saliva samples followed the method given by Nishita and colleagues (2009). DNA samples were then resuspended in Tris-EDTA buffer and quantified using Nanodrop ND-1000 1-position spectrophotometer (Thermo Scientific).

3.2.2.3. DNA amplification.

Samples of DNA were diluted to 50 ng/μL. DNA amplification was carried out following a modified version of that described by Erickson and colleagues (2008). Amplification of the 176 bp polymorphic *COMT* fragment used the primers COMT-F 5'-TCA CCA TCG AGA TCA ACC CC-3' and COMT-R 5'-GAA CGT GGT GTG AAC ACC TG-3'. Polymerase chain reaction (PCR) used 10X Taq buffer (2.5L μL), Taq polymerase (0.125 μL), dNTPs (5 nmol), primers (10 pmol each), Q solution (5 μL) and DNA (100 ng) made up to 25 μL with dH_2O. Denaturation occurred at 95 ºC for 15 min. There was then 30 cycles on a ThermoCycler (involving denaturation at 94 ºC for 30 s, annealing at 60 ºC for 30 s, and extension at 72 ºC for 30 s), followed by a final extension at 72 ºC.

3.2.2.4 Enzyme digestion.

PCR product (8 μL) was incubated with N1aIII for 1 hr at 37 ºC. Analysis of digestion products used a high-resolution agarose gel (4%) with a Quick Load 100 bp ladder (BioLabs) and a GelPilot Loading Dye (QIAGEN). DNA was immersed in an ethidium bromide solution for 10 s and then was visualized under ultraviolet light.

3.2.2.5 Genotyping.

Enzyme digestion resulted in bands of 82, 54 and 41 bp for the val^{158} allele and the 82 bp fragment was cut into 64 and 18 bp fragments for the met^{158} allele. Genotyping followed the method described by Erickson and colleagues (2008).

3.2.3 Face recognition memory

Face recognition was assessed using the Faces I subtest of the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). Participants were presented with a series of 24 faces, presented for 2 s each. They were requested to remember each face. Immediately after the presentation of this first series, they were serially presented with 48 images of faces. 24 of these were the previously encountered faces, while the 24 were new. Participants were asked to indicate whether they had previously encountered each face.

3.2.4 Data analysis

3.2.4.1 Data preparation.

Raw scores out of 48 on the Faces subtest were converted into percentage of correct responses for analyses. Observed *COMT* genotypes were consistent with those predicted by Hardy Weinberg equilibrium ($\chi^2 = 0.109$, $p > .05$). Of the 142 participants, 38 (26.8%) were

val homozygotes, 35 (24.6%) were met homozygotes and 69 (48.6%) were heterozygotes (val/met). Assumption testing on the data supported the use of parametric procedures.

3.2.4.2 Statistical analyses.

A two-way ANOVA was conducted on the face recognition scores, with *COMT* genotype (val/val; val/met; met/met) and sex as the between-subjects independent variables. Mean face recognition scores by *COMT* genotype and sex are shown in Table 3.1.

An additional two-way ANOVA was conducted on the face recognition scores, with *COMT* genotype at two levels (val allele and met/met) and sex as the between-subjects independent variables; descriptive data are shown in Table B2.1 and ANOVA results are shown in Table B2.2

3.3 Results

Results of the two-way ANOVA are shown in Table 3.2. There was a significant main effect of *COMT* genotype on face recognition ($F_{(2,136)} = 3.862$, $p = .023$). There was no significant main effect of sex ($p > .05$). There was however a significant two-way interaction between *COMT* genotype and sex on face recognition ($F_{(2,136)} = 7.631$, $p = .001$; Fig. 3.1). A supporting analysis with *COMT* treated as a dichotomous variable yielded consistent results (Table B2.2).

Simple effects tests using Bonferroni adjustments were carried out on the significant two-way interaction. The effect of *COMT* genotype for each sex was analysed first. Pairwise comparisons are displayed in Table 3.3. Of the male participants, met homozygotes ($\underline{M}$ = 86.6, *SE* = 2.87) achieved significantly higher face recognition scores than both heterozygotes ($\underline{M}$ = 77.6, *SE* = 1.80; $p = .028$) and val homozygotes ($\underline{M}$ = 70.7, *SE* = 2.64; *p*

< .001). The comparison between heterozygotes and val homozygotes was not significant (p < .05). For females, no differences between *COMT* genotypes were significant (p > .05). This suggests the main effect of *COMT* is best understood as an artefact of the interaction between genotype and sex. Secondly, the effect of sex for each *COMT* genotype was analysed. Pairwise comparisons are shown in Table 3.4. For val homozygotes, females ($\underline{M}$ = 82.6, SE = 1.91) achieved significantly higher scores than males ($\underline{M}$ = 70.7, SE = 2.64; p < .001). For heterozygotes and met homozygotes, there were no significant sex differences in face recognition (p > .05).

4. Discussion

Our results provide support for our hypothesis that *COMT* val^{158}met genotype and sex would interact to affect memory for faces. The *COMT* polymorphism only affected face recognition performance in male participants. Male met homozygotes outperformed both the male heterozygotes and the male val homozygotes. While there was no significant difference between the male heterozygotes and the male val homozygotes, this may be due to low statistical power and a dosage effect trend does appear to be emerging. Our hypothesis that there would be a main effect of sex on face recognition performance was not supported, and a sex difference in face recognition ability was only found for *COMT* val homozygotes, with females attaining higher scores. While there was an unexpected main effect of *COMT* genotype on face recognition, this was not consistently observed across the sexes and is thus better understood as an artefact of the interaction between genotype and sex.

The presence of an interaction between *COMT* val^{158}met genotype and sex on face recognition is consistent with other studies that have found sex to affect the impact of the *COMT* polymorphism on cognitive phenotypes (e.g., Barnett et al., 2007; Gurvich & Rossell,

Table 3.1

Mean Face Recognition Scores by COMT Genotype and Sex.

Sex	COMT	Mean	Std. Error	*N*
Male	Val/Val	70.7	2.64	13
	Val/Met	77.6	1.80	28
	Met/Met	86.6	2.87	11
	Total	77.8	1.43	52
Female	Val/Val	82.6	1.91	25
	Val/Met	80.8	1.50	41
	Met/Met	79.86	1.95	24
	Total	81.1	1.04	90
Total	Val/Val	78.5	1.63	38
	Val/Met	79.5	1.17	69
	Met/Met	82.0	1.74	35
	Total	79.9	.85	142

Table 3.2

Two-way ANOVA for Face Recognition Scores with COMT Genotype and Sex as the Between-Subjects Variables

Source	*F*	df	*p*
Sex	2.536	1	.114
COMT Genotype	3.862*	2	.023
COMT*Sex	7.631**	2	.001
Error		136	

*$p < .05$, ** $p < .01$

2015; O'Hara et al., 2006; Soeiro-De-Souza et al., 2013). O'Hara and colleagues (2006) reported an interaction between *COMT* and sex on verbal memory, with male val homozygotes outperforming heterozygote and met homozygote men while females did not differ as a function of genotype. This effect of *COMT* genotype on memory in male participants is inconsistent with our study, where a met advantage was documented. This inconsistency may be due to the difference in the form of memory being assessed, as well as the effects of *COMT* on cognition varying over the lifespan. O'Hara and colleagues (2006) examined cognition in older adults. Age related declines in dopamine receptor densities may reduce the amount of dopamine that is optimal for cognitive performance (Harris et al., 2005), although studies of *COMT* and cognition in older adults do not consistently support this shift (e.g., Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Nagel et al., 2008).

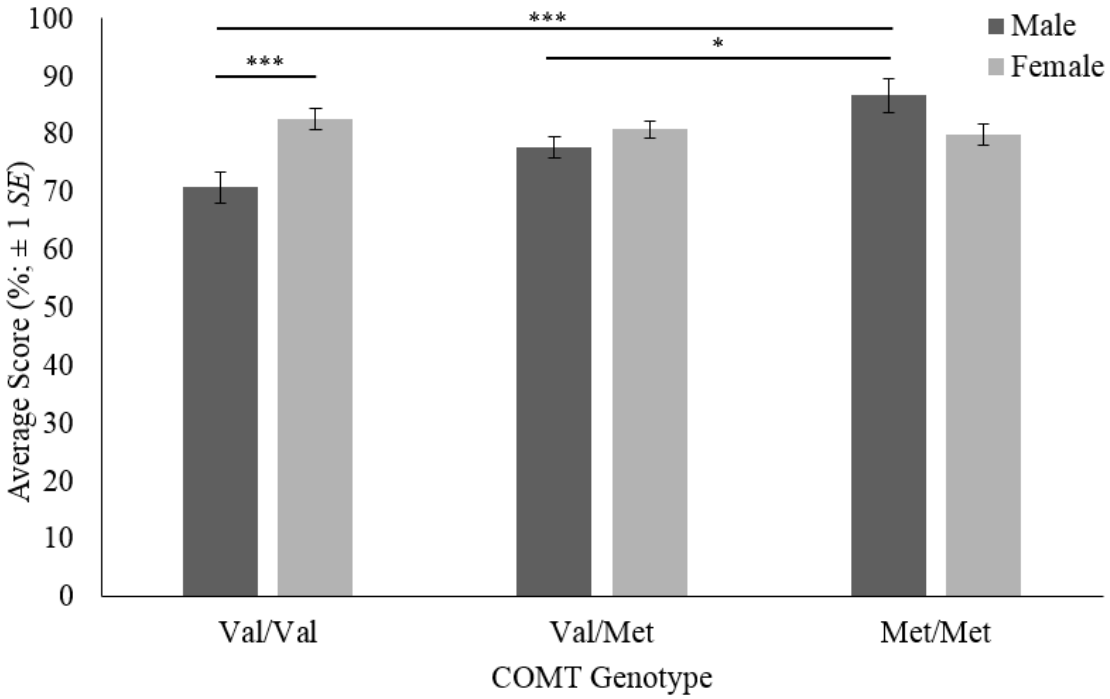

Fig. 3.1. Face recognition scores for *COMT* genotypes by sex.

The error bars are based on ± one standard error.

*$p < .05$, *** $p < .001$

Generally, studies with young adult samples that have found an association between *COMT* genotype and memory performance or executive function have reported higher scores in met allele carriers (Witte & Flöel, 2012). Our finding of a performance advantage in male met homozygotes relative to males with the val allele suggests that the lower levels of dopamine associated with the val allele are less conducive to face recognition. This fits with recent research linking dopamine to the functioning of the fusiform face area (Rypma et al., 2015). Furthermore, the effects of the COMT enzyme on dopamine are particularly pronounced in the prefrontal cortex (PFC; Chen, Lipska, et al., 2004) and neuroimaging research has implicated the lateral PFC of the right hemisphere in memory for faces (e.g., Druzgal & D'Esposito, 2003; Sergerie, Lepage, & Armony, 2005).

Table 3.3

Pairwise comparisons for COMT genotype at each level of sex.

Sex	Comparison	Mean difference	Std. Error	*p*
Male	Val/Val – Val/Met	-6.9	3.20	.096
	Val/Val – Met/Met	-15.9	3.91	.000
	Val/Met – Met/Met	-8.9	3.39	.028
Female	Val/Val – Val/Met	1.8	2.42	1.000
	Val/Val – Met/Met	2.7	2.72	.958
	Val/Met – Met/Met	1.0	2.45	1.000

Table 3.4

Pairwise comparisons for sex at each level of COMT genotype.

COMT	Comparison	Mean difference	Std. Error	*p*
Val/Val	Male – Female	-11.9	3.26	.000
Val/Met	Male – Female	-3.2	2.34	.170
Met/Met	Male – Female	6.7	3.47	.056

The male-specific effect of *COMT* genotype on face recognition is consistent with literature suggesting that some of the effects of *COMT* on cognition may be more pronounced in males (e.g., Barnett et al., 2007; Harrison & Tunbridge, 2008). In *COMT* knock-out mice, males show an increase in frontal dopamine while dopamine levels in females do not change (Gogos et al., 1998). Similarly, the effect of *COMT* genotype on COMT activity in human lymphocytes is stronger in males than in females (Chen, Lipska, et al., 2004). *COMT* genotype and enzyme activity may thus be less consequential for females, possibly due to hormone-regulated compensatory mechanisms in the neurotransmission or metabolism of catecholamines (Gogos et al., 1998).

Oestrogen has been shown to inhibit the expression of *COMT* mRNA and reduce the activity of the COMT enzyme (Cohn & Axelrod, 1971; Jiang et al., 2003; Xie et al., 1999), as well as enhancing dopamine synthesis and release (Becker, 1990, 2000; Pasqualini et al., 1995; Xiao & Becker, 1994). This appears to contribute to sex differences in the dopaminergic system. Research on COMT activity and thermal stability in the human liver has demonstrated significantly lower levels of COMT activity in females compared to males (Boudikova, Szumlanski, Maidak, & Weinshilboum, 1990). Similarly, COMT activity is lower for females than for males in the human PFC, independent of *COMT* genotype (Chen, Lipska, et al., 2004). In striatal and extrastriatal regions, levels of baseline dopamine and dopamine released in response to D-amphetamine are higher in women than men (Riccardi et al., 2006, 2011).

The current study demonstrated a sex difference in face recognition performance that was only present for *COMT* val homozygotes. Males have been shown to have higher levels of COMT activity than females in the human PFC, as well as for each individual genotype (Chen et al., 2004). Male val homozygotes thus have lower levels of synaptic dopamine than

their female counterparts. This particular genotype-sex combination may be associated with dopamine levels that are sub-optimal for performance on the face recognition task. Interestingly, the forms of cognition for which O'Hara and colleagues (2006) found *COMT* genotype-sex interactions are also abilities for which sex differences tend to traditionally manifest (Herlitz & Rehnman, 2008). Social experiences may perpetuate or mitigate the effects of differing dopamine levels.

It is possible that social experiences during development could also render male val homozygotes more vulnerable than female val homozygotes to showing poorer face recognition. Compared to that of boys, the socialisation of girls has tended to focus more on the promotion of emotional understanding and interpersonal sensitivity (McClure, 2000). This could encourage girls to pay greater attention to faces, which convey emotion, and boys may consequently have less cumulative experience with faces (McClure, 2000). Differences in socialisation may amplify early hormone-related sex differences in behaviour towards facial stimuli. Female infants of 12 months make significantly more eye contact with their parents than male infants of the same age (Lutchmaya, Baron-Cohen, & Raggatt, 2002). Research by Connellan and colleagues (2000) suggests that sex differences in preference for viewing faces over non-social objects may be present in neonates as early as one day after birth, with girls showing more interest in a face than a mobile (although see Alexander & Wilcox, 2012).

Male val allele carriers may also have less accumulated experience with faces than their met homozygote counterparts. Reduced availability of synaptic dopamine in *COMT* val homozygotes may disrupt the processing of reward information (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Wichers et al., 2008). This could result in the viewing of facial stimuli being less rewarding to val homozygotes and their attention to faces may thus be

reduced. Over the course of development, impaired social reward could interact with environmental factors to contribute to male val homozygotes having poorer face recognition ability in young adulthood. Differences in dopamine levels and experience with faces may be protective in female val homozygotes.

Uncertainty concerning the mechanisms underlying the *COMT* genotype-sex interaction is a limitation of our research. These are likely to be multifactorial and may affect different phenotypes in differing ways (Harrison & Tunbridge, 2008). As our sample consisted of young adults, it would be interesting to see if the genotype-sex interaction on face recognition is present in older adults. Oestrogen levels in postmenopausal women fall to below those of their male peers (Bjornerem et al., 2004), and research on an older sample may thus help to elucidate the mechanisms underlying the interaction in our study.

In the current study, we were unable to control for factors such as menstrual cycle phase and use of oral contraceptives in female participants, or other potentially influential variables such as ethnicity. Women taking oral contraceptives may have higher levels of COMT activity than other women (Briggs & Briggs, 1973) and, ideally, oral contraceptive use should be taken into account. In addition, the sample in the present study was of mixed ethnicity, while the effects of the *BDNF* and *COMT* polymorphisms may vary between ethnic groups (Shimizu et al., 2004; Wang et al., 2016). Further research on a larger sample could explore the potential effects of these variables on the interaction demonstrated in our study. Lastly, a limitation of our study was a relatively small sample size. This is particularly pertinent to consider given an interaction was being tested. Homozygotes were less frequently observed than heterozygotes and, when divided by sex, cell counts were low. There is a need for further large-*n* studies investigating the scope and nature of *COMT* genotype-sex interactions on cognition.

In conclusion, the current study is believed to be the first to demonstrate a male-specific effect of the *COMT* val^{158}met polymorphism on face recognition performance in healthy young adults. Male met homozygotes demonstrated a greater ability to determine whether faces had been previously encountered than male val carriers. A more rapid deactivation of synaptic dopamine in male val allele carriers may drive this effect. This study thus contributes to accumulating evidence of sex-specific effects of COMT on cognitive phenotypes. Sex-specific effects of the *COMT* polymorphism are likely to be obscured when sex-genotype interactions are not considered in analyses. Studies failing to consider these interactions may have contributed to inconsistencies in research on *COMT* and cognition.

While previous research has demonstrated a female advantage for performance on face recognition tasks, our study found a sex difference in face recognition for *COMT* val homozygotes only. Female *COMT* val homozygotes outperformed males of this genotype. Due to the down-regulation of COMT activity by oestrogen, males with the val/val genotype may have lower levels of dopamine that their female counterparts. This is consistent with a role for dopamine in our ability to recognise previously encountered faces. Hormones or social factors may interact with dopamine levels to facilitate performance in female val homozygotes. Future research may seek to explore potential sex differences in the effects of *COMT* genotype on PFC dopaminergic activity and how these concur with sex-specific effects on cognition.

Chapter 4: *BDNF*, Conscientiousness, and Recall

Preface

Individual differences in personality traits predict the behaviours one engages in and thus impact upon the experiences and environments they are exposed to (Briley & Tucker-Drob, 2014). These experiences and environments can in turn further reinforce those particular traits. After the age of 30 years, personality can be described as being predominantly stable (Terracciano, Costa, & McCrae, 2006).

The "Big Five", or Five Factor, model (e.g., Costa & McCrae, 1992) is a widely accepted framework for representing and researching personality (Mann, Briley, Tucker-Drob, & Harden, 2015). Supported by factor analysis (Roccas, Sagiv, Schwartz, & Knafo, 2002) and considered to be universal (e.g., Schmitt, Allik, McCrae, & Benet-Martínez, 2007; Yamagata et al., 2006, although see Gurven, von Rueden, Massenkoff, Kaplan, & Lero Vie, 2013), the Big Five basic dimensions of personality are commonly referred to as Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness (Costa & McCrae, 1992).

Of these traits, Conscientiousness has emerged as the strongest predictor of a range of health-related behaviours and experiences that may affect cognitive well-being and function (e.g., Goodwin & Friedman, 2006; Raynor & Levine, 2009). These include exercise, diet, drug and alcohol abuse, sleep quality, job success, community involvement and relationship stability (e.g., Raynor & Levine, 2009; Roberts, Walton, & Bogg, 2005). Consequently, Conscientiousness has been shown to be important in fortifying the brain against age-related structural changes and cognitive declines (e.g., Hock et al., 2014; Jackson, Balota, & Head, 2011; Wilson et al., 2015). While Conscientiousness does demonstrates a moderately high

degree of heritability (e.g., Bergeman et al., 1993; Jang, Livesley, & Vemon, 1996; Jang, McCrae, Angleitner, Riemann, & Livesley, 1998), it does not appear to be related to variation in the *BDNF* gene (Montag, 2014).

In the study that follows, the personality trait of Conscientiousness was tested as a potential moderator of our previously reported effect of the *BDNF* val^{66}met polymorphism on recall performance.

Impact of brain-derived neurotrophic factor (*BDNF*) val^{66}met on recall performance is moderated by conscientiousness

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Abstract

A single nucleotide polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene has been associated with hippocampal volume and memory performance. Conscientiousness has been inconsistently associated with performance on memory tasks, and high conscientiousness appears to confer protection against age-related cognitive decline. This study aimed to determine whether trait Conscientiousness moderates the effect of the *BDNF* val^{66}met polymorphism on recall performance in young adults. A sample of 102 young adults was assessed on Conscientiousness using the Revised NEO Personality Inventory (NEO PI-R) and immediate visual recall using the Family Pictures subscale of the Wechsler Memory Scale – Third Edition (WMS-III). The interaction term between Conscientiousness and *BDNF* genotype was a significant predictor of recall performance. The met allele was only associated with poorer recall performance when combined with low levels of Conscientiousness. Our results demonstrate the potential for modest genetic disadvantage on memory tasks to be overcome through a conscientious demeanour. Replication of this moderation using a larger sample size is warranted.

Keywords

Neurogenetics, BDNF, Recall, Conscientiousness, NEO PI-R

4.1 Introduction

Genes and personality both provide sources of variation that may be of consequence for our cognitive development. A single nucleotide polymorphism (SNP) in the gene that codes for brain-derived neurotrophic factor (BDNF) has been linked to individual differences in hippocampal volume (e.g., Hajek, Kopecek & Hoschl, 2012; Kambeitz et al., 2012; Molendijk et al., 2012) and recall performance (e.g., Egan et al., 2003; Hariri et al., 2003; Lamb, Thompson, McKay, Waldie & Kirk, 2015). The personality trait of Conscientiousness has also been linked, albeit inconsistently, to performance on memory tasks (e.g., Baker & Bichsel, 2006; Smith, Persyn & Butler, 2011) and may facilitate short-term neuroplasticity (Dima, Friston, Stephan, & Frangou, 2015). Interestingly, high Conscientiousness appears to reduce age-related declines in grey matter (e.g., Jackson, Balota, & Head, 2011) and memory (e.g., Wilson, Schneider, Arnold, Bienias, Bennett, 2007), suggesting that Conscientiousness may have protective effects on cognitive function. The present study investigated the joint effect of the *BDNF* val^{66}met SNP and Conscientiousness on recall performance in young adults.

BDNF is a neurotrophin that promotes the growth and differentiation of neurons during the development of the nervous system (Huang & Reichardt, 2003; Lessmann, Gottmann & Malcangio, 2003; Poo, 2001). BDNF also encourages neurogenesis in the dentate gyrus of the mature brain (Mohapel, Frielingsdorf, Haggblad, Zachrisson & Brundin, 2005; Thakker-Varia et al., 2014) and appears to be crucial for long-term potentiation (LTP; Panja & Bramham, 2014; Poo, 2001), a form of synaptic plasticity. LTP provides a potential mechanism through which BDNF secretion may affect memory and learning (Egan et al., 2003; Lamb et al., 2014).

In the gene coding for BDNF, the val^{66}met polymorphism produces a non-conservative substitution of a valine (val) amino acid for a methionine (met; Chen, Patel, et al., 2004; Egan et al., 2003). In a European population, 64% are val homozygotes (val/val), 34% are heterozygotes (val/met), and 3% are met homozygotes (met/met; HapMap-CEU). The met allele appears to reduce activity-dependent BDNF secretion and alter intracellular trafficking of the protein (Egan et al., 2003). Cumulative effects of reduced BDNF can be seen in adult neuroanatomy and neurophysiology. Recent meta-analyses have generally reported an effect of BDNF on hippocampal volume, with lower hippocampal volumes present in those with the met allele (Hajek, Kopecek & Hoschl, 2012; Kambeitz et al., 2012; Molendijk et al., 2012, although see Harrisberger et al., 2014). Consistent with the apparent effects of BDNF in the hippocampus, behavioural studies have found the met allele to be associated with poorer declarative memory (Kambeitz et al., 2012). This may be due to individuals with the met allele having impaired synaptic events and consequently forming weaker memory traces (Hariri et al., 2003). In a recent study by Thompson and colleagues (2013), healthy young adults carrying the met allele displayed lower levels of LTP than val homozygotes.

Presence of the met allele does not invariably result in poorer memory performance. Indeed, the effects of the *BDNF* polymorphism alone are modest. Certain personality traits have also been found to explain variation in cognition. One of these is Conscientiousness, a trait that is considered to "reflect the ability and tendency of individuals to inhibit or constrain impulses to [instead] follow rules or pursue non-immediate goals" (DeYoung et al., 2010, p. 2). A number of large studies have reported significant negative correlations between conscientiousness and intelligence (e.g., Moutafi, Furnham, & Crump, 2003; Moutafi, Furnham, & Paltiel, 2004). It has been argued that less able individuals operating within a competitive environment might develop higher levels of conscientiousness in order to

compensate and meet performance demands (Moutafi et al., 2003; Moutafi et al., 2004). Despite this inverse relationship between conscientiousness and intelligence, high conscientiousness has emerged as the most important personality trait in predicting academic success (e.g., Chamorro-Premuzic & Furnham, 2003; Higgins, Peterson, Pihl & Lee, 2007; Komarraju, Karau & Schmeck, 2009; Noftle & Robins, 2007).

Gold and Arbuckle (1990) theorised that Conscientiousness should positively affect performance on cognitive tasks requiring greater attention and cognitive effort. They suggested that individuals high in Conscientiousness process incoming information in a more elaborate, organised manner. This in turn may make information more accessible in the future. Consistent with this, high Conscientiousness has been associated with the use of effective learning strategies (Komarraju, Karau, Schmeck & Avdic, 2011).

Research into the effects of conscientiousness on memory performance has yielded mixed results however. A study by Smith and colleagues (2011) found a positive effect of conscientiousness on memory for target events. Similarly, Aiken-Morgan and colleagues (2012) found that Competence and Self-discipline, two facets of Conscientiousness, were positively associated with verbal learning and working memory. While Baker and Bichsel (2006) found Conscientiousness to be positively associated with short-term memory in a group of cognitively superior older adults, although this association was not present in their sample of younger adults. A number of other studies have reported no effect of Conscientiousness on memory (e.g., Sanford & Fisk, 2009; Süb, Oberauer, Wittmann, Wilhelm, & Schulze, 2002).

Despite mixed results at the behavioural level, recent research has associated Conscientiousness with the neural substrates of memory and learning. Whittle and colleagues (2008) demonstrated that adolescents with high effortful control, a characteristic comparable

to Conscientiousness, have larger hippocampi. DeYoung and colleagues (2010) have reported that lateral prefrontal cortex (PFC) volumes are greater in individuals with higher levels of conscientiousness. The lateral PFC is considered to be important for controlled memory retrieval (Cabeza & St Jacques, 2007). A recent study by Dima and colleagues (2015) looked at effective connectivity, an indirect measure of short-term plasticity at the neural network level, during a working memory task. They found that Conscientiousness facilitated task-related neuroplastic responses, while the trait Neuroticism inhibited them. A relationship between Conscientiousness and neuroplasticity provides a mechanism through which Conscientiousness may affect memory across the lifespan.

There is promising evidence to suggest Conscientiousness may protect against age-related cognitive impairments and dementias. High Conscientiousness has been associated with a lower risk of developing Mild Cognitive Impairment (MCI) and lower levels of age-related cognitive decline (e.g., Chapman et al., 2012; Duberstein et al., 2011; Wilson et al., 2007). Similarly, high Conscientiousness has been associated with higher cognitive performance in a sample of centenarians (Martin, Baenziger, MacDonald, Siegler, & Poon, 2009). A recent meta-analysis of case-control and longitudinal studies on the effects of personality on dementia concluded that Conscientiousness reduces dementia risk (Low, Harrison, & Lackersteen, 2013). This is consistent with the finding that highly conscientious individuals show reduced age-related grey matter decline in areas including the parahippocampus (e.g., Jackson, Balota, & Head, 2011) and is perhaps due to the healthier lifestyles of conscientious individuals.

The aim of the present study was to determine whether Conscientiousness moderates the relationship between the *BDNF* val^{66}met polymorphism and recall performance in young

adults. It was hypothesised that high levels of Conscientiousness may provide a buffer against the poorer memory performance that has been previously documented in met allele carriers.

4.2 Material and methods

4.2.1 Participants

A sample of 102 young adults aged between 18 and 34 years (M = 22.2, SD = 3.4) participated in this study. Of these participants, 68 were female. Self-reported ethnicities were European or Pakeha (64%), Asian (18%), Indian (13%), Middle Eastern (1%) and Mixed (5%). All participants had either normal or corrected-to-normal vision and gave their informed consent for inclusion in this study.

4.2.2 Genotyping

4.2.2.1 DNA collection.

Participants were each requested to provide a small saliva sample. These samples were collected using Oragene-DNA Self Collection kits following the method specified by the manufacturer.

4.2.2.2 DNA extraction.

DNA was extracted from the saliva samples following the method given by Nishita and colleagues (2009). DNA samples were resuspended in Tris-EDTA buffer and then quantified using Nanodrop ND-1000 1-position spectrophotometer (Thermo Scientific).

4.2.2.3 DNA amplification.

The DNA samples were diluted to 50 ng/μL. DNA amplification followed a modified version of the method described by Erickson and colleagues (2008). Amplification was carried out on the 113 bp polymorphic *BDNF* fragment, using the primers BDNF-F 5'-GAG GCT TGC CAT CAT TGG CT-3' and BDNF-R 5'-CGT GTA CAA GTC TGC GTC CT-3'. Polymerase chain reaction (PCR) was conducted using 10X Taq buffer (2.5L μL), Taq polymerase (0.125 μL), dNTPs (5 nmol), primers (10 pmol each), Q solution (5 μL) and DNA (100 ng) made up to 25 μL with dH_2O. PCR conditions consisted of denaturation at 95 ºC for 15 min, 30 cycles on a ThermoCycler (involving denaturation at 94 ºC for 30 s, annealing at 60 ºC for 30 s, and extension at 72 ºC for 30 s) and a final extension at 72 ºC.

4.2.2.4 Enzyme digestion.

PCR product (6.5 μL) was incubated with Pm1l overnight at 37 ºC. A high-resolution agarose gel (4%) with a Quick Load 100 bp ladder (BioLabs) and a GelPilot Loading Dye (QIAGEN) was used to analyse the digestion products. After 10min of immersion in an ethidium bromide solution, DNA was visualized under ultraviolet light.

4.2.2.5 Genotyping.

Enzyme digestion resulted in a 113 bp fragment for the met^{66} allele, cut into 78 bp and 35 bp fragments for the val^{66} allele as described by Erickson and colleagues (2008).

4.2.3 Personality measurement

The full Revised NEO Personality Inventory (NEO PI-R; Costa & McCrae, 1992) was administered. The NEO PI-R consists of 240 statements which participants respond to on a 5-point Likert scale. Of these statements, 48 contribute to an overall Conscientiousness score

out of 192 possible points. As the present study was hypothesis-driven, only the trait of Conscientiousness was analysed.

4.2.4 Recall measurement

Recall performance were assessed using the Family Pictures I subtest from the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). This taps into immediate visual memory. In this task, participants are introduced to a fictional family that consists of seven members. They are then presented with four scenes, each shown for 10 s. Each scene depicts four of the family members engaging in specific activities in unique spatial locations. Immediately subsequent to the viewing of these, participants were asked set questions that assessed their memory of the scenes. These questions related to the activities and locations of each character. The Family Pictures subtest measures recall, requiring the retrieval of contextualised details of the scenes from memory. A recent study reported that *BDNF* val homozygotes outperform met allele carriers on the Family Pictures subtest (Lamb et al., 2015).

4.2.5 Data analysis

4.2.5.1 Data preparation.

Observed *BDNF* genotypes were consistent with those predicted by Hardy Weinberg equilibrium ($\chi^2 = 0.154$, $p > .05$). Of the 102 participants, 50 (49.0%) were val (G) homozygotes, 8 (7.8%) were met (A) homozygotes, and 44 (43.1%) were heterozygotes (val/met; G/A).

As expected, preliminary analyses showed no relationship between BDNF genotype and Conscientiousness ($p > .05$). Prior to further analyses and calculation of an interaction term, the continuous predictor variables were centred to avoid the problem of

multicollinearity. Tests for multicollinearity indicated that a low level of multicollinearity was present (VIF values < 2). Assumption testing indicated that our data were suitable for parametric procedures.

For the main analysis, BDNF genotype was tested at three levels in order to examine a potential dose effect of the met allele.

4.2.5.2 Statistical analyses.

A hierarchical linear multiple regression was performed on the data to examine Conscientiousness as a moderator of the association between *BDNF* genotype and recall performance (percentage correct in the Family Pictures task). *BDNF* genotype (val/val; val/met; met/met) and Conscientiousness were entered in the first step of the regression analysis. The interaction term between genotype and Conscientiousness was entered in the second step of the regression analysis.

Mean recall and Conscientiousness scores for *BDNF* genotypes are shown in Table 4.1.

An additional hierarchical linear multiple regression was performed on the data to examine Conscientiousness as a moderator of the association between *BDNF* genotype and recall performance, with genotype at two levels (val/val and met allele) rather than three. The results of this regression are displayed in Appendix B (Table B3).

4.3 Results

Results of the hierarchical regression are shown in Table 4.2. At Step 1, *BDNF* genotype and Conscientiousness accounted for a significant amount of variance in recall

performance (R^2 = .059, $F_{(2,99)}$ = 3.131, p = .048). Neither predictor had a significant main effect on recall performance (p > .05).

At Step 2 of the regression, the interaction term between BDNF genotype and Conscientiousness explained a significant increase in variance in recall performance (ΔR^2 = .044, $F_{(1, 98)}$ = 4.757, p = .032). The interaction term was a significant predictor of recall performance (b = .208, $t_{(98)}$ = 2.181, p = .032), as was Conscientiousness (b = .208, $t_{(98)}$ = 2.885, p = .005). The overall model was significant (R^2 = .103, $F_{(3, 98)}$ = 3.752, p = .013).

Simple slopes were used to explore the nature of the significant interaction. These were tested for high levels of Conscientiousness (1 SD above the mean), average Conscientiousness (the mean) and low levels of Conscientiousness (1 SD below the mean). The simple slope for low Conscientiousness showed a significant relationship between BDNF genotype and recall performance (b = -8.117, SE_b = 3.026, $t_{(98)}$ = 2.682, p = .009), while the slopes for average (b = -3.083, SE_b = 2.004, $t_{(98)}$ = 1.539, p > .05), and high Conscientiousness were not significant (b = 1.951, SE_b = 3.086, $t_{(98)}$ = .632, p > .05). These simple slopes are plotted in Figure 4.1.

For the sake of completeness, simple slopes were also created for the effect of Conscientiousness on recall performance at each level of *BDNF* genotype (treated as a 3-level categorical variable). The slope for the *BDNF* val/met (b = 0.187, SE_b = 0.081, $t_{(96)}$ = 2.301, p = .024) genotype was significant, while the slopes for the val/val (b = 0.009, SE_b = 0.072, $t_{(96)}$ = 0.124, p > .05) and met/met (b = 0.587, SE_b = 0.322, $t_{(96)}$ = 1.82, p > .05) genotypes were not. When *BDNF* genotype was treated as a categorical variable with two levels (val/val versus met allele carriers), the simple slope for the *BDNF* met allele carriers was significant (b = 0.210, SE_b = 0.079, $t_{(98)}$ = 2.677, p = .009), while the slope for the val/val genotype was not (b = 0.009, SE_b = 0.072, $t_{(98)}$ = 0.124, p > .05) (Figure 4.2).

Table 4.1

Mean Recall and Conscientiousness Scores for BDNF Genotypes

	Val/Val *N* = 50		Val/Met *N* = 44		Met/Met *N* = 8				
Variable	Mean	SD	Mean	SD	Mean	SD	*F*	df	*p*
Recall	77.33	11.04	73.99	14.31	70.51	19.10	1.329	2	.270
Conscientiousness	111.78	25.66	108.89	24.21	108.88	15.10	.179	2	.836
Error								99	

4.4 Discussion

Results supported our hypothesis that Conscientiousness would protect against poorer memory performance in *BDNF* met allele carriers, moderating the relationship between genotype and memory. In the present study, *BDNF* genotype alone did not significantly predict variation in recall performance, perhaps due to low statistical power. *BDNF* genotype was only detrimental to recall when the met allele was accompanied by low levels of Conscientiousness. This finding is consistent with previous research suggesting that Conscientiousness facilitates plasticity in young adults (Dima et al., 2015) and protects against age-related cognitive decline and dementias (e.g., Chapman et al., 2012; Duberstein et al., 2011; Low et al., 2013; Wilson et al., 2007). When the significant interaction term was

Table 4.2

Results of Hierarchical Regression Analysis for Variables Predicting Recall Performance

	Step 1			Step 2		
Variable	*B*	*SE B*	β	*B*	*SE B*	β
BDNF Genotype	-3.170	2.041	-.152	-.3120	2.003	-.149
Conscientiousness	.100	.053	.183	.208	.072	.380***
Genotype x Conscientiousness				.208	.095	.287**
R^2		.059			.103	
F for ΔR^2		3.131*			4.757**	

*p = .048, **p = .032, ***p = .005

included in the regression model, Conscientiousness also emerged as a significant predictor of recall performance.

The route through which Conscientiousness may protect against poor memory performance is not yet certain. Conscientiousness is a key predictor of an individual's engagement in various health-related behaviours that may have cumulative effects on cognition over their lifetime. Booth and colleagues (2014) found that the effect of Conscientiousness on brain integrity was partially mediated by health behaviours. Consequently, the relationship between Conscientiousness and memory is likely to be

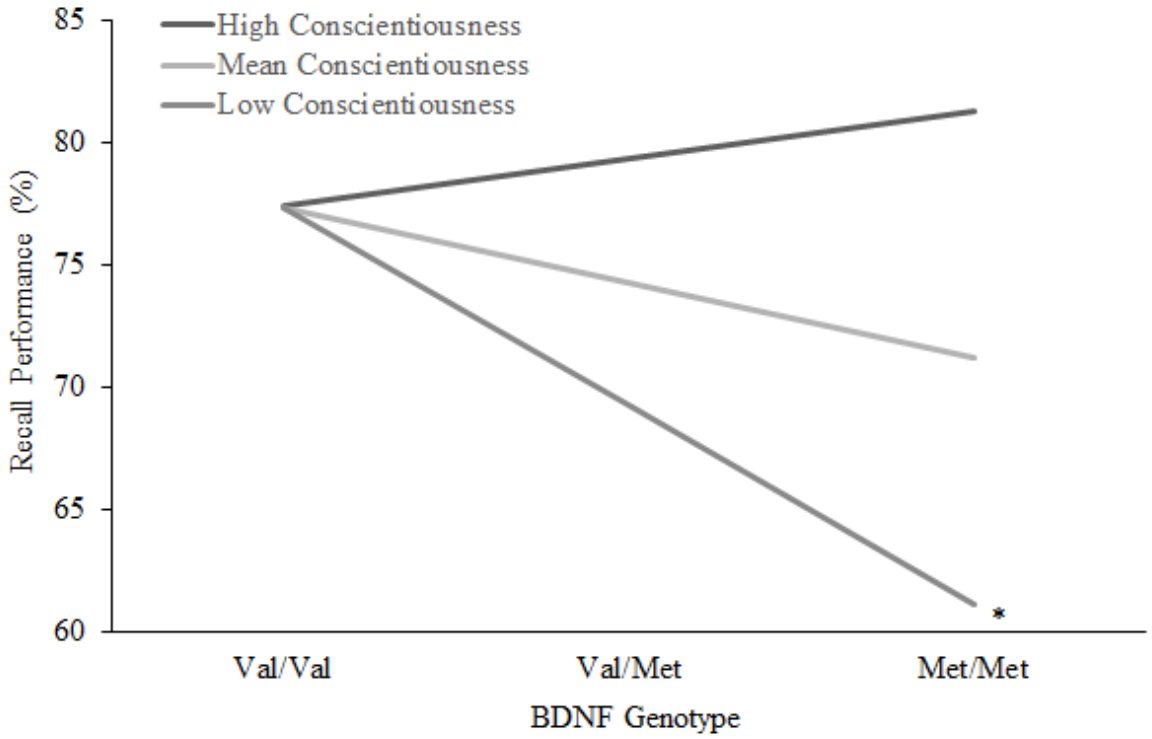

Fig. 4.1. Simple slopes for the association between *BDNF* genotype and recall performance at each level of Conscientiousness.

*$p < .05$ for slope.

mediated at least in part by the behaviours that Conscientiousness predicts. For example, Conscientiousness is inversely related to tobacco use (Bogg & Roberts, 2004). Nicotine decreases neurogenesis in the dentate gyrus of the hippocampus (Abrous et al., 2002) and has been associated with impaired working memory and verbal memory in adolescent users (Jacobsen et al., 2005).

Physical activity is another health-related behaviour that offers a plausible route through which Conscientiousness may confer protection against cognitive decline and memory deficits. Studies suggest conscientious individuals may be more likely to engage in

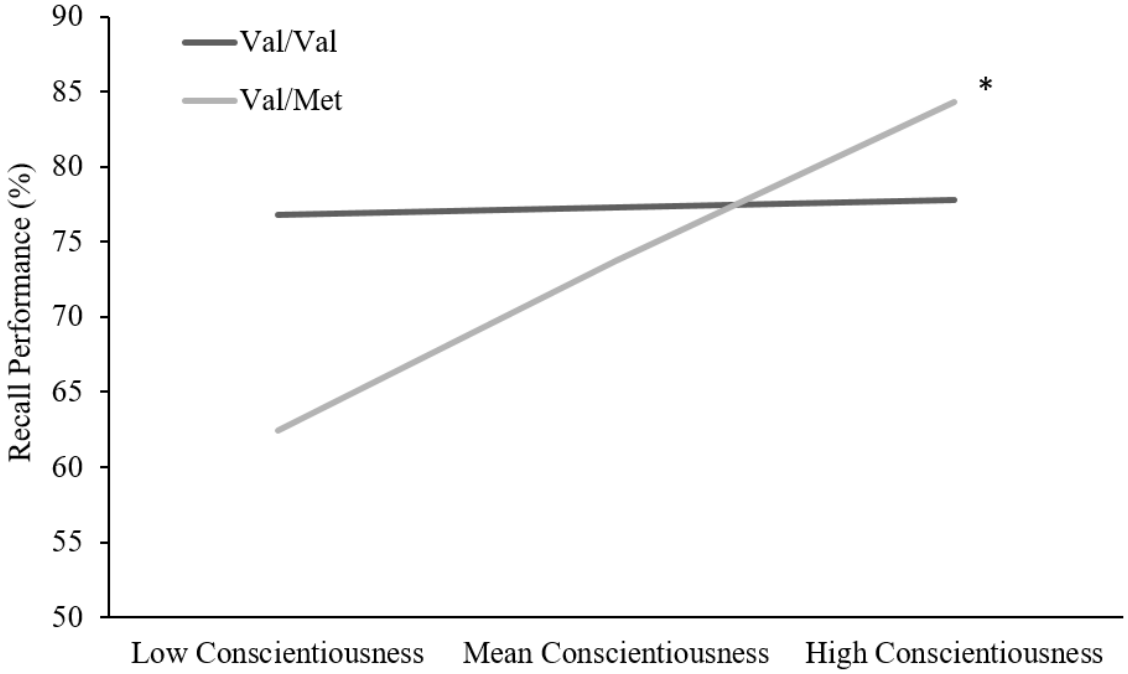

Fig. 4.2. Simple slopes for the effect of Conscientiousness on recall performance at each level of *BDNF* genotype.

*$p < .01$ for slope.

regular physical activity (for a review see Bogg & Roberts, 2004). This relationship may be attributed to an overarching construct such as mental wellbeing, positively correlated with Conscientiousness, which is associated with greater engagement in positive health-related behaviours such as exercise (Gatt, Burton, Schofield, Bryant, & Williams, 2014).

There is now substantial evidence for physical activity promoting plasticity and memory in the mammalian brain. Aerobic exercise has been found to increase levels of BDNF in healthy humans (Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014). In mice, exercise increases angiogenesis, spine density, dendritic branching and synaptic plasticity

(Wang & van Praag, 2012). Neurogenesis in the dentate gyrus is also enhanced. A recent study by Smallwood and colleagues (2015) found that long-term potentiation (LTP)-like changes in visual-evoked potentials last for a longer duration in more physically active young adults. Exercise has been reported to moderate the effect of age on medial temporal lobe volume in older adults, protecting against volume declines (e.g., Bugg & Head, 2011). Similarly, Chaddock and colleagues (2010) found hippocampal volumes were greater in children with higher fitness levels. Hippocampal volume mediated the positive relationship between fitness and relational memory.

Consistent with the effects of physical activity on neuroplasticity, Déry and colleagues (2013) also found that individuals who increased their fitness during an aerobic exercise programme showed reduced memory interference during a pattern recognition task, perhaps attributable to increased neurogenesis. In contrast, individuals with depressive tendencies exhibited deficits on the task (Déry et al., 2013). Depressive tendencies, negatively associated with Conscientiousness (Kotov, Gamez, Schmidt, & Watson, 2010), have also been linked to reduced hippocampal volumes (Bremner et al., 2014). This is perhaps a consequence of elevated glucocorticoid levels in depressed individuals. In sum, the associations between Conscientiousness and health variables affecting neuroplasticity and memory may result in plasticity being bolstered in conscientious met allele carriers.

Cognitive techniques employed by conscientious individuals may have given them an advantage when approaching our memory task. Komarraju, Karau, Schmeck, and Avdic (2011) found that Conscientiousness was positively correlated with the use of various effective learning strategies including elaborative processing, fact retention, methodical study, and synthesis-analysis. Highly conscientious individuals are more likely to report using memory techniques such as mnemonics and applying effort when performing memory

tasks (de Frias, Dixon, & Bäckman, 2003). The Family Pictures visual recall task gave participants a very limited amount of time to process and store information from each image. Concentration and effective utilisation of learnt memory strategies could allow relatively conscientious met allele carriers to compensate for the otherwise poorer memory capabilities that are manifest in less conscientious carriers. A limitation of our study is that participants did not report on how they approached the memory task.

Further limitations of the present study are the small sample size and lack of data on health-related behavioural variables. Due to our small sample size and expected low count of met homozygotes, the results of the present study should be considered with caution and replication of the moderation effect in a larger sample would be desirable. A greater number of met homozygotes could confirm the dosage effect emerging in the present study. As the val and met alleles are thought to be co-dominant, heterozygotes are likely to present intermediate phenotypes (Chen, Patel, et al., 2004). In an additional analysis of the data from the present study, in which *BDNF* genotype treated as a dichotomous variable, the interaction term between *BDNF* and Conscientiousness was only approaching significance (Table B3). A larger sample would have also allowed for potentially influential variables such as ethnicity to be accounted for; the sample in the present study was of mixed ethnicity and the effects of the *BDNF* and *COMT* polymorphisms may be expected to vary between ethnic groups (Shimizu et al., 2004; Wang et al., 2016). Furthermore, the present study did not examine the mechanisms that may underlie the interaction between *BDNF* genotype and Conscientiousness on memory. While we theorise that health-related variables may mediate the relationship through bolstering plasticity in conscientious met allele carriers, no data on these variables were collected.

In conclusion, we found that Conscientiousness moderates the relationship between *BDNF* genotype and recall performance in a sample of young adults. Poorer recall performance was only observed in met allele carriers who were low in Conscientiousness. This suggests that moderate to high levels of Conscientiousness may be protective in met allele carriers, perhaps through facilitating the use of compensatory cognitive strategies or increasing the likelihood of health-related behaviours that boost neuroplasticity. Our results demonstrate the potential for personality factors to affect the manifestation of a modest genetic disadvantage. Due to our limited sample size, we urge caution and suggest replication of this moderation effect in a larger sample is necessary.

Chapter 5: Gene-Environment Interaction Impacts on Intelligence

Preface

For a more complete understanding of the relationships between genes and cognition, the importance of environmental variables must be taken into account and potential gene-environment interactions considered (Goldberg & Weinberger, 2004). In some situations, gene-environment interactions account for higher levels of variation in cognitive ability than the main effects of genes. For example, Caspi and colleagues (2007) found that while the FADS2 gene had no direct impact on child IQ, this gene moderates the relationship between breastfeeding and IQ. Gene-environment interactions may contribute to the difficulty around establishing and replicating genetic effects on cognitive ability.

There is some indication that effects of *COMT* genotype on psychological phenotypes may be greatest in individuals exposed to environmental stressors (e.g., Ramsay et al., 2013; Simons et al., 2009). Stressors that occur early in development may be particularly influential for outcomes (Heim & Binder, 2012). The following study used longitudinal data from the Auckland Birthweight Collaborative (ABC) study to examine whether an environmental stressor, namely exposure to antenatal maternal stress, would amplify effects of *COMT* variants on child IQ scores.

Perceived stress during pregnancy and the catechol-*O*-methyltransferase (*COMT*) Rs165599 polymorphism impacts on childhood IQ

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Abstract

Maternal stress during pregnancy has been associated with a range of adverse outcomes in offspring and the catechol-*O*-methyltransferase (COMT) gene has been linked to differential susceptibility to the consequences of antenatal stress. This study examined two functional polymorphisms of the COMT gene (Rs4680 and Rs165599) in relation to maternal perceived stress and childhood cognitive performance. Data from the longitudinal Auckland Birthweight Collaborative (ABC) study was used. Maternal perceived stress over the prior month was measured at birth, 3.5 and 7 years. Full-Scale IQ (FSIQ) was measured at ages 7 and 11. At age 11, a total of 546 DNA samples were collected from the child participants. Data were subjected to a series of split-plot ANOVAs with birthweight for gestational age as a covariate. There were direct effects of maternal stress during the last month of pregnancy on offspring FSIQ at ages 7 and 11 years. A significant interaction revealed that children exposed to high maternal antenatal stress had significantly lower FSIQ scores at both 7 and 11 years of age than those exposed to low stress, only when they were carriers of the Rs165599 G allele. At each age, this difference was of approximately 5 IQ points. The G allele of the Rs165599 polymorphism may confer genetic susceptibility to negative cognitive outcomes arising from exposure to antenatal stress. This finding highlights the need to consider gene-environment interactions when investigating the outcomes of antenatal stress exposure.

KEY WORDS: Intelligence, Gene-environment, Longitudinal, Maternal stress, Child development

5.1 Introduction

Antenatal events can have enduring effects on offspring outcomes. Of such events, maternal antenatal stress has surfaced as a variable that can have particularly potent influences on both physical and psychological development (Beydoun & Saftlas, 2008; Talge, Neal & Glover, 2007; Van den Bergh, Mulder, Mennes, & Glover, 2005). Genetic susceptibility is likely to moderate the relationship between antenatal stress and detrimental psychological and cognitive outcomes (Caspi & Moffitt, 2006). Polymorphisms in the gene coding for catechol-*O*-methyltransferase (COMT) are a likely candidate for this, given this gene has been previously linked to differential functioning of the hypothalamic-pituitary-adrenal (HPA) system and stress sensitivity (Walder et al., 2010).

A range of independent prospective studies have provided compelling evidence that antenatal maternal stress is connected to social/emotional and cognitive outcomes during infancy and childhood (for a review, see Talge et al., 2007). With stressors in the antenatal environment having particularly formative effects on development (Barker, 1998), genetic vulnerabilities to stressors may be especially relevant at this point in time (e.g., Thompson et al., 2012). Davis and colleagues (2004) found maternal symptoms of depression and anxiety during the antenatal period to predict heightened behavioural reactivity in infancy, while controlling for postnatal depression and anxiety levels. Beyond infancy, the adverse outcome most consistently associated with antenatal stress has been the greater likelihood of attention deficit hyperactivity disorder (ADHD) symptoms, detected in early childhood (O'Connor, Heron, Golding, Beveridge & Glover, 2002), late childhood (Van den Bergh & Marcoen, 2004) and mid-adolescence (Van den Bergh et al., 2005). These effects were found despite controlling for a number of potentially confounding variables including postnatal anxiety and birthweight for gestational age.

Relatively less research has explored the implications of exposure to antenatal maternal stress for offspring intelligence, with studies having generally been confined to studying these during infancy and early childhood. Huizink, Robles de Medina, Mulder, Visser, and Buitelaar (2003) found that a greater number of daily hassles during early gestation predicted lower scores on the Bayley Mental Development Index (MDI) at 8 months of age, as did high levels of pregnancy-specific anxiety during mid-gestation. Neither of these associations had been present at 3 months of age, although MDI scores at this age were negatively correlated with measurements of early morning cortisol taken from the mothers during late pregnancy. Similar results have come from a retrospective study by LaPlante and colleagues (2004), who investigated cognitive development in children whose mothers had been pregnant during a natural disaster; the 1998 ice storm in Quebec, Canada. These toddlers attained lower MDI and language development scores when compared to standardised norms. Levels of antenatal stress exposure accounted for 11% of the variance in their Bayley MDI score and 12% of the variance in their productive language score. This was after variables already known to be associated with MDI scores (e.g., birth weight), and language production (e.g., age at testing), were taken into account. Furthermore, those exposed to higher levels of antenatal stress were found to have lower Full-Scale IQ (FSIQ) and Verbal IQ (VIQ) scores in a follow-up testing phase when the children were 5 years of age (LaPlante, Brunet, Schmitz, Ciampi, & King, 2008). This suggests that the impact of antenatal stress on cognition is not a transient phenomenon and may extend further into child development, although more research is needed to confirm this.

Genetic differences could help explain the considerable variation observed in the manifest outcomes of prenatal exposure to maternal stress. Not all children are adversely affected by exposure to antenatal stress and those that are affected differ in both the type and severity of the cognitive or behavioural outcome. It is possible that variation in the *COMT*

gene could mediate interactions with exposure to antenatal stress and cognitive outcomes in the child. Located on chromosome 22, this gene codes for an enzyme that catalyses the metabolism of released catecholamines in the prefrontal cortex (PFC) (Egan et al., 2001).

Catecholamines such as dopamine and noradrenaline are implicated in the HPA axis stress response (Snider & Kuchel, 1983), which is correlated with average basal noradrenaline activity (Young, Abelson & Cameron, 2005). In the PFC the release of both dopamine and noradrenaline increases during stress exposure (Finlay, Zigmond & Abercrombie, 1995). The common val^{158}met polymorphism (Rs4680) of the *COMT* gene, in which a single G/A base pair substitution leads to a valine (val) to methionine (met) substitution at codon 158, results in activity of the COMT enzyme being reduced to a quarter of what was originally encoded by the val allele (Lachman et al., 1996). Met carriers have been demonstrated to have higher extracellular dopamine levels in the PFC (Chen, Lipska, et al., 2004). Research by Oswald, McCaul, Choi, Yang, and Wand (2004) has linked the val^{158}met polymorphism to HPA response magnitude. A role for COMT in stress vulnerability is further supported by the findings of Thompson and colleagues (2012), who examined the val^{158}met polymorphism and its association with maternal perceived stress and behavioural difficulties in ABC children. They found, when compared to the other children, that those with two copies of the met allele had higher levels of emotional and behavioural problems, but only if they were exposed to antenatal maternal stress. This gene-environment interaction suggests that an absence of the val allele confers a genetic susceptibility to adverse emotional and behavioural outcomes following stress in utero (Thompson et al., 2012).

Consistent with the role that COMT plays in the PFC, there is also evidence to suggest that the *COMT* gene may affect cognitive function. Variation in the *COMT* gene has

been demonstrated to predict normal variation in executive function (e.g., Malhotra et al., 2002; Egan et al., 2001) and processing speed (e.g., Bilder et al., 2002), as well as episodic and semantic memory (de Frias et al., 2004). However, it should be noted that such associations have not been consistently observed. Barnett, Scoriels and Munafò (2008) conducted a meta-analysis of the effects of the *COMT* val^{158}met polymorphism on various cognitive phenotypes. Although there was a robust (albeit small) association between IQ and genotype, the polymorphism was found to have no association with the majority of the phenotypes, which included measures of memory and executive function.

COMT variants other than the val^{158}met polymorphism are also expressed in the human brain and may be involved in the regulation of COMT expression (Bray et al., 2003). In concordance, variants at several loci have been found to affect cognitive function in children (Barnett, Heron, Goldman, Jones & Xu, 2009). The Rs165599 single nucleotide polymorphism (SNP) is located downstream of the *COMT* gene and involves an A allele being switched for a G allele. While RNA expression of the G allele is on average 24% lower than that of the A allele, it is uncertain whether this confers a comparable difference in levels of the COMT protein and what the implications may be for enzyme activity (Bray et al., 2003). The Rs165599 G allele has been found to be overrepresented in schizophrenia (Shifman et al., 2002) and bipolar disorder (Burdick et al., 2007), although this is not consistently observed (Greenwood et al., 2011). It has also been linked to poorer performance on a verbal memory task (Burdick et al., 2007). Within a clinical population, Chan and colleagues (2005) found G homozygotes to perform significantly worse on measures of visual memory and prefrontal executive function than A homozygotes and heterozygotes (although see Soronen et al., 2008).

As the PFC continues to mature through childhood and adolescence (Giedd, 2004), effects of the *COMT* gene on cognition may vary with age. Barnett and colleagues (2007) examined the effects of the *COMT* val^{158}met polymorphism on cognitive performance in a sample of pubescent and prepubescent children. In the boys alone, there were significant effects of genotype on executive function and verbal IQ. Interestingly, effects on IQ were greater in pubescent boys than in those who had not yet entered puberty. Similarly, a recent study of children and adolescents found that benefits of the Rs4680 met allele for visuospatial working memory did not emerge until after ten years of age (Dumontheil et al., 2011). Further age-specific effects of *COMT* variance have come out of research by Gaysina and colleagues (2013), although these effects did not withstand correction for multiple testing. Given this accumulating evidence, it may be useful to measure cognitive phenotypes at multiple ages when examining the effects of variance in the *COMT* gene.

The purpose of the current study was to investigate the association between maternal stress and childhood cognitive performance of offspring with and without the Rs165599 risk allele (G) and/or the Rs4680 met allele, using data from a longitudinal study in New Zealand. The aims were to determine (1) whether antenatal maternal stress is associated with IQ scores of offspring at 7 and/or 11 years of age; (2) whether maternal stress at 3.5 and/or 7 years after birth is associated with IQ scores of offspring at 7 and/or 11 years of age; and (3) whether such associations differ between Rs165599 or Rs4680 genotypes. It was hypothesised that children exposed to higher levels of antenatal maternal stress would exhibit lower IQ scores at 7 and 11 years of age, thus extending the findings of LaPlante and colleagues (2004; 2008) into late childhood. Consistent with previous research with this sample (Thompson et al., 2012), we also hypothesised that the cognitive performance of children with the Rs165599 risk allele (G) and/or the Rs4680 met allele would be more affected by antenatal maternal stress than children without. These effects were predicted to be specific to the programming

effects of maternal stress experienced in the antenatal period, with maternal stress in the time after this appearing less critical (e.g., Bergman, Sarkar, O'Connor, Modi & Glover, 2007; Pianta & Egeland, 1994).

5.2 Methodology

5.2.1 Participants

A detailed description of the Auckland Birthweight Collaborative (ABC) Study is available elsewhere (Thompson et al., 2001). In brief, babies born between 16 October 1995 and 30 November 1997 who were resident in the Auckland Healthcare region of Auckland, New Zealand were eligible for inclusion in the study. Babies born between 16 October 1995 and 12 August 1996 who were resident in the Waitematā Health region of Auckland were also eligible, with recruiting in this region ceasing at an earlier date due to changes in the region's recording policy that meant reliable obstetric records were no longer available. Infants were excluded from the study if they were preterm (having completed less than 37 weeks of gestation), from a multiple pregnancy, delivered at home, or had congenital abnormalities thought to affect birthweight or later development.

All eligible infants born small for gestational age (SGA; $\leq 10^{th}$ percentile for sex and gestation) were included in the study. A random sample of eligible infants with birthweights appropriate for gestational age (AGA) was also selected, such that the SGA and AGA groups had similar numbers. Estimations of gestational age were carried out using the date of the late menstrual period, if this was available and gave rise to an age within two weeks of the best clinical estimate of gestational age at birth. If not, the best clinical estimate was used. The study consisted of 1714 participants at birth, of whom 871 had mothers who self-reported as being of European ethnicity.

The study has followed up on the participants at a number of intervals, with data on a range of variables being collected at the approximate ages of 1, 3.5, 7 and 11 years. At the early follow-up phases (1 year, 3.5 years) there was a poor response rate for the non-European ethnicities, raising concerns about the generalisability of results in these populations. Consequently, the later follow-ups have only included those whose mothers self-reported as being of European ethnicity. From the original sample, the response rate for Europeans was 63.1% at the 3.5 year phase, 67.9% at the 7 year phase and 71.1% at the 11 year phase. At the follow-up phase when participants were 11 years of age, 546 (63%) of them provided either a sample of peripheral blood (n = 397) or a buccal swab (n = 149) for purposes of DNA extraction. Of these participants, 227 (42%) were participants that had been allocated to the SGA group and 319 (58%) were from the AGA group.

Each phase of the study received ethical approval from the Auckland Regional Ethics Committee. Signed consent for the study and the extraction of DNA was given by the parents of the child participants, with the participants themselves in assent.

5.2.2 Cognitive Testing

Cognitive ability of the child participants was assessed at the 7 year follow-up phase through the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991). The WISC-III takes approximately 60 minutes to complete and requires no reading or writing from the participant. Scores from 10 sub-tests are used to create an overall Full-Scale Intelligence Quotient (FSIQ) score.

At the 11 year follow-up phase cognitive ability was again assessed, this time using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The WASI requires approximately 30 minutes to be administered and scores from four sub-tests give rise to a FSIQ score. At both phases of cognitive testing, the trained examiners were blind to the

birth weight status, maternal perceived stress scores and genetic data connected to the participant.

5.2.3 Maternal Stress

The 10-item version of the Perceived Stress Scale (PSS-10; Cohen & Williamson, 1988) was employed to assess maternal perceived stress. The items in the PSS-10 inquire about the degree to which one appraises their life to have been unpredictable, over-loaded and uncontrollable over the month prior to the testing. Consequently, it can be used to investigate the contribution of non-specific stress to the aetiology of disease and psychological disorders. The PSS-10 has been found to have adequate internal reliability (Cohen & Williamson, 1988) and construct validity (Roberti, Harrington & Storch, 2005). It is an economical scale that is quick to administer. The questions posed are easy to understand, as are the various response alternatives. Each question in the PSS-10 requires a response on a 5-point Likert scale that ranges from 0 ("Never") to 4 ("Very Often"), indicating the frequency of certain feelings or thoughts over the course of the previous month. The resulting composite scores range from 0 to 40, with higher sores signalling greater perceived stress.

The PSS-10 was administered at birth, 3.5 and 7 years to the mothers of the child participants. In cases where someone other than the mother accompanied the child to one of the follow-up sessions, data from that family were excluded from the analyses. This was due to the information provided by the accompanying adult not being comparable to the maternal stress data that was previously collected, and resulted in data being lost from 11 families at 3.5 years and 29 families at 7 years.

5.2.4 Genotyping

DNA was extracted from the blood and buccal samples using Qiagen's DNA extraction kit. Genotyping was then performed via the Sequenom MassARRAY iPlex genotyping platform (Sequenom, San Diego, CA), which uses MALDI-TOF mass spectrometry to identify the SNP allele (Gabriel, Ziaugra & Tabbaa, 2009). Procedures were conducted in accordance with the recommendations of the manufacturers. The SNP of interest was in a multiplex with SNPs from another study using the same samples. The sample plates each contained DNA samples from the ABC study and duplicate samples, as well as blanks and reference samples from the Centre d'Etude du Polymorphisme Humain (CEPH; The International HapMap Consortium, 2003).

For the Rs4680 SNP, independent double genotyping was employed for quality control, blind to both the sample identity and the other caller. In addition, CEPH genotypes were compared to those in HapMap. The observed genotype frequencies did not differ from those predicted by Hardy Weinberg equilibrium ($\chi^2 = 3.828$, $p > .05$). Of a total of 469 successfully genotyped individuals, 119 (25.6%) were met (A) homozygotes, 137 (29.0%) were val (G) homozygotes and 213 (45.4%) were heterozygotes (val/met; G/A).

For the Rs165599 SNP, comparisons between our observed genotypes and the CEPH genotypes could not be made due to the latter data being unavailable. However, independent double genotyping was employed for quality control. The observed genotype frequencies did not differ from those predicted by Hardy Weinburg equilibrium ($\chi^2 = 2.332$, $p > .05$). Of a total of 532 successfully genotyped individuals, 252 (47.4%) were A homozygotes (A/A), 41 (7.7%) were G homozygotes (G/G), and 239 (44.9%) were heterozygotes (A/G).

5.2.5 Statistical Analysis

5.2.5.1 Data preparation

Due to the small sample size, Rs165599 genotypes were dichotomised into those with at least one copy of the G allele (the G homozygotes and the heterozygotes) and the A homozygotes, thus isolating the risk allele. G homozygotes did not significantly differ from the heterozygotes on any of our measured variables ($p > .05$). For purposes of the analyses, Rs4680 genotypes were dichotomised into those with at least one copy of the met allele (the Met homozygotes and the heterozygotes) and the val homozygotes. Met homozygotes did not significantly differ from the heterozygotes on any of our measured variables ($p > .05$).

Maternal stress scores at each phase were dichotomised into scores lower than or equal to the median maternal stress score for that phase and those higher than the median. Median maternal stress scores were 13, 13 and 12 for birth, 3.5 and 7 years respectively.

5.2.5.2 Analyses for Rs4680

For each of the three phases at which maternal perceived stress was assessed, FSIQ scores were subjected to a split-plot ANOVA with maternal stress (low and high) and genotype (met allele and val/val) as between-subjects independent variables and age (7 years and 11 years) as the within-subjects independent variable. In order to control for birthweight, birthweight for gestational age (SGA and AGA) was included as a dichotomous covariate.

5.2.5.3 Analyses for Rs165599

For each of the three phases at which maternal perceived stress was assessed, FSIQ scores were subjected to a split-plot ANOVA with maternal stress (low and high) and genotype (G allele and A/A) as between-subjects independent variables and age (7 years and 11 years) as the within-subjects independent variable. In order to control for birthweight,

birthweight for gestational age (SGA and AGA) was included as a dichotomous covariate. Mean FSIQ scores at each level of the independent variables are provided in Table 5.1.

5.2.5.4 Control analyses

A further ANOVA (run on FSIQ scores with maternal stress and Rs165599 genotype as between-subjects independent variables and age as the within-subjects independent variable) controlled for both birthweight for gestational age (SGA and AGA) and maternal school leaving age (3 levels; younger than 16 years, 16 years, and older than 16 years). Finally, to control for the Rs4680 SNP, this analysis was run again with both birthweight for gestational age (SGA and AGA) and Rs4680 genotype (val/val and met allele) as covariates. All statistical analyses were conducted using IBM SPSS Statistics software (version 19.0).

Statistical significance was defined using an alpha level of .05. All post-hoc tests used Bonferroni adjustments.

5.2.5.5 Additional analyses

In a supporting analysis with Rs165599 genotype at three levels rather than dichotomised, FSIQ scores were subjected to an split-plot ANOVA with antenatal maternal stress (low and high) and genotype (G/G, G/A, A/A) as between-subjects independent variables and age (7 years and 11 years) as the within-subjects independent variable. Birthweight for gestational age (SGA and AGA) was included as a dichotomous covariate. Mean FSIQ scores at each Rs165599 genotype are provided in Table B4.1; results of the ANOVA are displayed in Table B4.2.

Hierarchical regressions with FS1Q at age 7 and age 11 as dependent variables were conducted to examine antenatal maternal stress as a continuous variable; centred Rs165599

Table 5.1

Mean Full-Scale IQ Scores for Ages 7 and 11 Years at Each Level of the Independent Variables.

Independent Variable	Level	Age					
		7 Years			11 Years		
		N	Mean	Std. Error	*N*	Mean	Std. Error
Rs4680	Val/Val	122	108.4	1.33	137	109.8	1.26
	Met	299	110.9	.76	331	110.3	.75
Rs165599	G	250	110.2	.85	279	110.6	.79
	A/A	224	110.1	.91	252	109.7	.89
Maternal stress	High	210	108.4	.93	223	107.4	.92
(birth)	Low	375	110.7	.69	378	111.6	.67
Maternal stress	High	194	109.2	.87	202	109.1	.99
(3.5 years)	Low	299	110.3	.83	283	111.1	.78
Maternal stress	High	271	108.7	.79	248	108.6	.83
(7 years)	Low	315	110.9	.77	288	111.6	.81
Total		588	109.9	.55	603	110.1	.55

genotype (G/G, G/A, A/A), centred antenatal maternal stress and birthweight for gestational age (SGA and AGA) were entered in the first step of the analysis. The interaction term between centred Rs165599 genotype and centred antenatal maternal stress was entered in the second step. Results are displayed in Tables B4.3 and B4.4.

5.3 Results

5.3.1 Results for Rs4680

5.3.1.1 Perceived stress during pregnancy

The split-plot ANOVA showed a significant main effect of maternal stress ($F_{(1,413)}$ = 4.323, p = .038). On average, significantly higher FSIQ scores were obtained by the children with low maternal stress ($\underline{M}$ = 111.1, SE = 0.85) than those with stress ($\underline{M}$ = 108.0, SE = 1.18). In addition, there was a significant main effect of age ($F_{(1,413)}$ = 4.634, p = .032). On average, significantly lower IQ scores were obtained at age 7 ($\underline{M}$ = 109.3, SE = 0.77) than at age 11 ($\underline{M}$ = 109.8, SE = 0.77). There was also a significant two-way interaction between age and the birthweight for gestational age covariate ($F_{(1,413)}$ = 6.003, p = .015). No other effects were significant.

5.3.1.2 Perceived stress at 3.5 years

The split-plot ANOVA showed a significant main effect of age ($F_{(1,355)}$ = 4.449, p = .015). On average, significantly lower IQ scores were obtained at age 7 ($\underline{M}$ = 110.0, SE = 0.81) than at age 11 ($\underline{M}$ = 110.5, SE = 0.81). There was a significant two-way interaction between age and Rs4680 genotype ($F_{(1,355)}$ = 6.574, p = .011). There was also a significant two-way interaction between age and the birthweight for gestational age covariate ($F_{(1,355)}$ = 5.682, p = .018). No other effects were significant.

Simple effects tests were run on the significant two-way interaction. When the effect of Rs4680 genotype at each level of age was tested, no comparisons were significant. The effect of age at each level of genotype was examined next. For children without the met allele, IQ was significantly higher at age 11 ($\underline{M}$ = 110.7, SE = 1.37) than at age 7 ($\underline{M}$ = 108.8, SE = 1.37; p = .045). The comparison for children with the met allele was not significant.

5.3.1.3. Perceived stress at 7 years

The split-plot ANOVA showed a significant main effect of maternal stress ($F_{(1,414)}$ = 4.097, p = .044). On average, significantly higher FSIQ scores were obtained by the children with low maternal stress ($\underline{M}$ = 111.2, SE = 0.89) than those with stress ($\underline{M}$ = 108.4, SE = 1.08). There was also a significant main effect of age ($F_{(1,414)}$ = 5.952, p = .015). On average, significantly lower IQ scores were obtained at age 7 ($\underline{M}$ = 109.5, SE = 0.75) than at age 11 ($\underline{M}$ = 110.1, SE = 0.75). There was a significant two-way interaction between age and the birthweight for gestational age covariate ($F_{(1,414)}$ = 5.847, p = .016). No other effects were significant.

5.3.2 Results for Rs165599

5.3.2.1 Perceived stress during pregnancy

The split-plot ANOVA showed a significant main effect of maternal stress ($F_{(1,466)}$ = 5.384, p = .021). On average, significantly higher FSIQ scores were obtained by the children with low maternal stress ($\underline{M}$ = 111.3, SE = 0.73) than those with stress ($\underline{M}$ = 108.5, SE = 0.95). There was a significant main effect of birthweight for gestational age ($F_{(1,466)}$ = 4.701, p = .031). Results also revealed a significant three-way interaction between age, genotype and maternal stress ($F_{(1,466)}$ = 4.720, p = .030). No other effects were significant. The results of the omnibus ANOVA are shown in Table 5.2. A supporting analysis with Rs165599 genotype at three levels (G/G, G/A and A/A) yielded consistent results (Table B4.2). Hierarchical regressions examining antenatal maternal stress as a continuous variable did not find significant interactions between Rs165599 and antenatal stress exposure (Tables B4.3 and B4.4); these regressions were unable to capture the repeated measures (FSIQ at ages 7 and 11 within one analysis) nature of the split-plot ANOVA design.

Table 5.2

Omnibus Split-Plot ANOVA for IQ Scores with Rs165599 Genotype and Antenatal Maternal Stress as the Between-Subjects Variables, Birthweight for Gestational Age as a Covariate, and Age as the Within-Subjects Variable.

Source	*F*	df	*p*
Age	1.987	1	.159
Rs165599	.002	1	.962
Antenatal Stress	5.384*	1	.021
Birthweight for Gestation	4.701*	1	.031
Age*Rs165599	1.932	1	.165
Age*Antenatal Stress	2.173	1	.141
Age*Birthweight for Gestation	3.004	1	.084
Rs165599*Antenatal Stress	2.195	1	.139
Age*Antenatal Stress*Rs165599	4.720*	1	.030
Error		466	

*$p < .05$

In order to run simple effects tests on the significant three-way interaction, the data were split by genotype. The interaction effect for carriers of the G allele, shown in Fig. 5.1(A), was analysed first. When the effect of age at each level of maternal stress was tested,

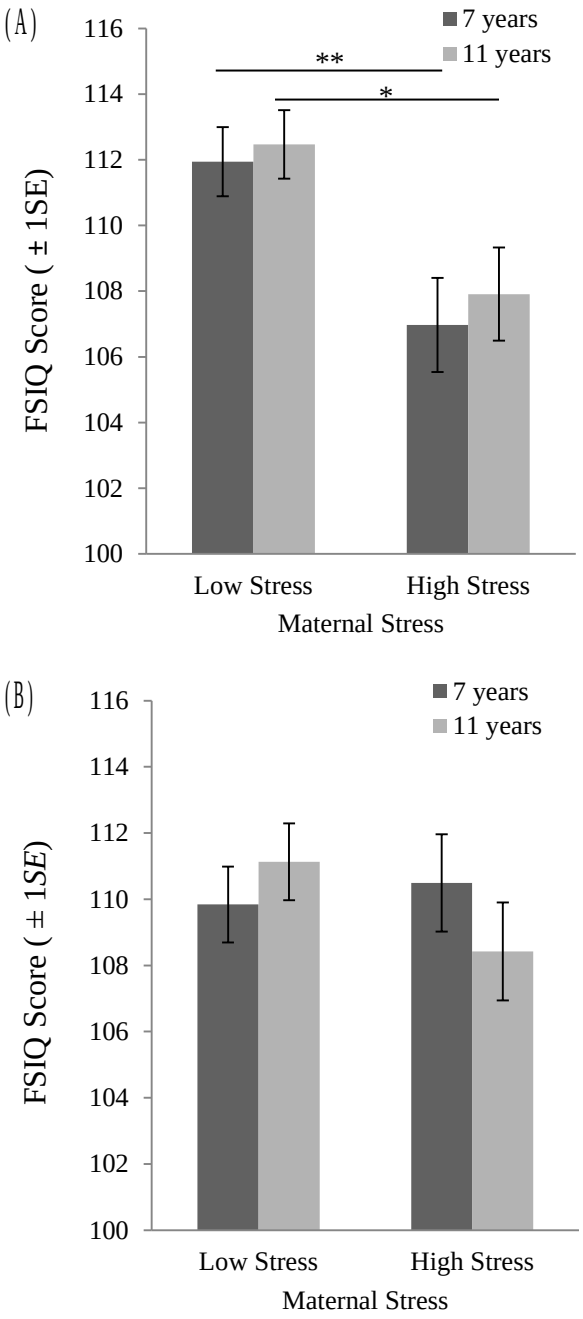

Fig. 5.1. (A) FSIQ scores at ages 7 and 11 years for Rs165599 G allele children of mothers with low and high stress at birth. (B) FSIQ scores at ages 7 and 11 years for Rs165599 A/A children of mothers with low and high stress at birth.

The error bars are based on ± one standard error.

*$p < .05$ **$p < .01$

no comparisons were significant. The effect of maternal stress at each level of age was then examined. At age 7, FSIQ scores were significantly higher for children whose mothers perceived low stress ($\underline{M}$ = 111.9, *SE* = 1.06) than those whose mothers perceived high stress ($\underline{M}$ = 106.9, *SE* = 1.42; *p* = .006). At age 11, FSIQ scores were also significantly higher for children whose mothers experienced low stress ($\underline{M}$ = 112.4, *SE* = 1.04) than high stress ($\underline{M}$ = 107.8, *SE* = 1.42; *p* = .011). As shown in Fig. 5.1(B), no comparisons were significant in the analysis for A homozygotes.

5.3.2.2 Perceived stress at 3.5 years

The split-plot ANOVA revealed a significant main effect of maternal stress ($F_{(1,402)}$ = 3.913, *p* = .049). On average, the children whose mothers reported lower levels of stress achieved significantly higher FSIQ scores ($\underline{M}$ = 111.8, *SE* = 0.83) than the children of those reporting higher stress ($\underline{M}$ = 109.3, *SE* = 0.97). No other effects were significant.

5.3.2.3 Perceived stress at 7 years

The split-plot ANOVA showed a significant main effect of maternal stress ($F_{(1,468)}$ = 6.450, *p* = .011). On average, significantly higher FSIQ scores were obtained by the children with low maternal stress ($\underline{M}$ = 111.7, *SE* = 0.79) than those with high maternal stress ($\underline{M}$ = 108.7, *SE* = 0.86). No other effects were significant.

5.3.2.4 Control analyses

In the ANOVA with both birthweight for gestational age and maternal education as covariates, there was a significant main effect of maternal stress ($F_{(1,461)}$ = 4.341, *p* = .038). On average, significantly higher FSIQ scores were obtained by the children with low maternal stress ($\underline{M}$ = 111.1, *SE* = 0.72) than those with stress ($\underline{M}$ = 108.6, *SE* = 0.95). There was also a significant main effect of the maternal education covariate ($F_{(1,461)}$ = 9.979, *p* =

.002). The interaction between age, Rs165599 genotype and antenatal maternal stress remained significant ($F_{(1,461)} = 4.101$, $p = .043$).

In the ANOVA with both birthweight for gestational age and Rs4680 genotype as covariates, there was a significant main effect of maternal stress ($F_{(1,402)} = 5.002$, $p = .026$). On average, significantly higher FSIQ scores were obtained by the children with low maternal stress ($\underline{M} = 111.3$, $SE = 0.80$) than those with stress ($\underline{M} = 108.3$, $SE = 1.06$). In addition, there was a significant main effect of age ($F_{(1,402)} = 6.638$, $p = .010$). On average, significantly lower IQ scores were obtained at age 7 ($\underline{M} = 109.7$, $SE = 0.71$) than at age 11 ($\underline{M} = 109.9$, $SE = 0.71$). There was a significant two-way interaction between age and the birthweight for gestational age covariate ($F_{(1,402)} = 7.022$, $p = .008$). The three-way interaction between age, Rs165599 genotype and antenatal maternal stress was approaching significance ($F_{(1,402)} = 3.792$, $p = .052$).

5.4 Discussion

Support was found for the hypothesis that exposure to antenatal maternal stress has an adverse impact on the cognitive development of the offspring, evident in the main effect of maternal antenatal stress on IQ scores. This result is consistent with previous studies that have found antenatal stress to be associated with poorer cognitive performance in early childhood (Huizink et al., 2003; LaPlante et al., 2004; LaPlante et al., 2008). It expands upon this literature by showing that the effects of antenatal stress on cognition are still evident in mid-childhood and early adolescence; early cognitive disadvantages are not fully overcome over the course of development. The consequences of antenatal stress for cognition are therefore not transient.

We found that maternal perceived stress when study members were 3.5 and 7 years of age had significant effects on childhood FSIQ scores. Higher maternal stress was associated with lower FSIQ scores, irrespective of Rs165599 genotype. Maternal stress has not consistently been found to be associated with offspring IQ (e.g., Pianta & Egeland, 1994), possibly due to variations in the measurement of stress and the age at which intelligence is assessed. However, higher perceived maternal stress may be indicative of a more stressful family environment, which could hinder learning and cognitive development in the child. As the differences were only of approximately 3 IQ points, it is unlikely that the poorer performance of the children was driving the maternal stress scores.

Of particular interest was the hypothesised significant interaction between age, Rs165599 genotype and antenatal maternal stress. At both 7 and 11 years of age, antenatal maternal stress was associated with significantly lower IQ scores in children with at least one copy of the Rs165599 G allele. At each testing phase, the difference was of approximately 5 IQ points. The presence of this gene-environment interaction supported our hypothesis that the G allele would act as a risk allele, increasing vulnerability to the environmental stressor. This follows from previous research implicating *COMT* variation in stress susceptibility (Thompson et al., 2012) and the Rs165599 G allele in both psychopathology (e.g., Burdick et al., 2007; Shifman et al., 2002) and poorer cognitive performance (e.g., Burdick et al., 2007; Chan et al., 2005). Contrary to our hypothesis, there was no effect of Rs4680 on the association between IQ and maternal stress at either age. There was also no direct effect of Rs4680 on IQ at either age. This may have been due to low statistical power in our study.

There are a number of plausible routes through which the *COMT* Rs165599 polymorphism and antenatal maternal stress could interact to affect cognitive performance. It is possible that a small increase in cortisol exposure may be sufficient to affect the

functioning of the HPA axis in the developing foetus, leading to a permanently deregulated stress response (Glover, O'Connor, & O'Donnell, 2010). This could have further implications for the catecholamine systems that are involved in HPA activity (Tsigos & Chrousos, 2002). Variation in the *COMT* gene may modulate the effects of antenatal stress exposure on HPA axis function, thus influencing levels of cortisol in the developing brain. Two mechanisms have been suggested to underlie this relationship (Oswald et al., 2004). The first of these implicates hypothalamic corticotropin-releasing hormone (CRH) release, which is likely to be greater in individuals with higher catecholaminergic activity. The second involves *COMT* genotypes indirectly affecting HPA activity through influencing the dopamine-mediated regulation of opioid transmission. Consistent with this, Zubieta and colleagues (2003) found that *COMT* Rs4680 met homozygotes show greater μ-opioid receptor binding potential in response to stress; the *COMT* Rs165599 polymorphism has not been investigated in this context.

In further support of a theoretical relationship between *COMT* variation and HPA axis function, recent research by Walder and colleagues (2010) demonstrated salivary cortisol levels during adolescence varied as a function of *COMT* val^{158}met genotype. *COMT* val^{158}met genotype also affected the trajectory that cortisol levels took between the initial study phase and the one-year follow-up phase, with met homozygotes displaying greater increases during this period of neurodevelopment; potential effects of the *COMT* Rs165599 polymorphism were not studied. Altered functioning of the HPA axis, as measured by cortisol secretion, could in turn have implications for cognitive performance. When in excess, glucocorticoids appear to cause learning difficulties and hippocampal damage in rodents (Luine, Villegas, Martinez, & McEwen, 1994). In research involving healthy human participants, higher cortisol levels have been similarly associated with poorer performance on memory tasks (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien et al., 1997).

Both glucocorticoids and catecholamines may influence the process of long-term potentiation (LTP). LTP describes a long-lasting increase in synaptic plasticity that is thought to be the molecular basis of memory and learning (Bliss & Collingridge, 1993; Cooke & Bliss, 2006). Levels of dopamine affect LTP induction in the PFC, with both insufficient and excessive dopamine being detrimental (Xu et al., 2009). An inverted U-shape relationship also exists between corticosterone (the main glucocorticoid in rodents) and LTP (Kerr, Huggett & Abraham, 1994), consistent with the finding that acute stress can impair the induction of LTP (Diamond & Rose, 1994; Maroun & Richter-Levin, 2003; Shors, Gallegos & Breindl, 1997). LTP induction may be important for the formation of activity-dependent synapses in early neurodevelopment (Durand, Kovalchuk & Konnerth, 1996), which could in turn have implications for later cognitive function (McAllister, 2007).

As hypothesised, there was no interaction between Rs165599 or Rs4680 genotype and perceived maternal stress on IQ when perceived stress was measured at 3.5 or 7 years of age. This aspect is comparable with the results of Thompson and colleagues (2012), who found that while antenatal maternal stress interacted with the *COMT* val^{158}met polymorphism to affect behavioural outcomes, maternal stress at 3.5 and 7 years of age did not. It appears that genetic vulnerability to the effects of maternal stress may be of greatest consequence when in the antenatal environment. Gestation is a critical developmental period characterised by sensitivity to antenatal exposures (Barker, 1998). The PFC, which plays a crucial role in higher-order cognitive abilities, is particularly susceptible to the negative impacts of stress exposure (Arnsten, 2009). This region of the brain differentiates relatively late in gestation (Kostović, Judaš, Petanjek, & Šimić, 1995; Mrzljak, Uylings, Kostović, & Van Eden, 1988). During the third trimester, there is a growth spurt in dendritic development in the PFC (Mrzljak et al., 1988). Exposure to glucocorticoids can modulate the proliferation and differentiation of cells (Wong & Herbert, 2006), as well as affecting synapse formation

(Antonow-Schlorke, Schwab, Li, & Nathanielsz, 2003). This disturbance is likely to interact with genetic make-up to shape the structure and function of the developing regions.

The present study has a number of limitations. The multiple testing in this study raises the possibility of a Type I error. Results should therefore be interpreted with caution and replication is necessary. It should also be noted that the present study had low statistical power (e.g., observed power for the three-way interaction was only 58.2%) and consequently less ability to correctly reject a null hypothesis.

Furthermore, as our sample included genetically related mothers and offspring, there is the chance that heritable factors are influencing both maternal predispositions to stress and offspring cognition. This possibility is difficult to address and to do so would require a genetically-sensitive research design such as prenatal cross-fostering (Rice et al., 2010). One way to partially control for common genetic factors is to adjust for maternal IQ, but these data were not available in the present study. When maternal education was entered into a control analysis as a proxy, the interaction between maternal stress, Rs165599 genotype and age remained significant. However, the possibility of passive gene-environment correlation remains a limitation of this study.

There was also no data available on maternal perceived stress for the month following the birth. If a mother is experiencing high levels of stress in the month prior to the delivery, she may continue to be stressed postpartum (Talge et al., 2007). This postnatal stress could affect the quality of the early parenting and environmental stimulation the infant receives. Bergman and colleagues (2007) noted that postnatal stress, unlike antenatal stress, had no significant effect on Bayley MDI scores in infancy. However, as the present study did not examine stress in the immediate postnatal period it remains possible that postpartum stress exposure could be interacting with Rs165599 genotype to affect cognitive outcomes rather

than this effect being specific to the antenatal environment. Similarly, there were moderate to high correlations between our measures of stress and consequently the main effects stress in one period may be at least partially mediated by stress in another.

As we did not collect data on maternal personality, the extent to which the personality trait of Neuroticism (Negative Affect) was underlying the gene-environment interaction (rather than merely stress in a specific time-frame) could not be determined. Scores on the PSS have been shown to correlate with Neuroticism (Ebstrup, Eplov, Pisinger, & Jørgensen, 2011), a trait that demonstrates heritability (Pedersen, Plomin, McClearn, & Friberg, 1988). Consequently, what appears to be a gene-environment interaction may in fact be a gene-gene or gene-trait interaction. It is, however, worth noting that gene-environment interactions were not found for maternal stress as measured when the child was 3.5 or 7 years of age.

In the present study, the average maternal stress scores observed at each testing phase were consistent with U.S. norms (Cohen & Williamson, 1988). These stress levels were sufficient to produce an interaction with the Rs165599 polymorphism. It could be the case that the Rs165599 polymorphism is of greater consequence in European populations. The effects of *COMT* on susceptibility to schizophrenia, for example, are more consistently observed in samples with European ancestry than those of Asian descent (Glatt, Faraone & Tsuang, 2003). Replication in a non-European sample may be useful in establishing the generalisability of our results.

In conclusion, the present study contributes to the existing literature on the effects of antenatal maternal stress on cognitive outcomes through using data from the longitudinal ABC study. It provides evidence that suggests the effects of antenatal stress on intelligence are enduring and can be observed into early adolescence, corroborating previous studies that have focused on infancy and early childhood. The interaction between Rs165599 genotype

and antenatal maternal stress supports the possibility that variation in the *COMT* gene may confer genetic susceptibility to negative outcomes arising from exposure to antenatal stress. This study is believed to be the first to report an interaction between antenatal maternal stress and variation in the *COMT* gene affecting cognitive performance. It highlights the need to consider gene-environment interactions when investigating the outcomes of antenatal stress exposure. Further research should seek to further elucidate the relationship between COMT and stress hormones in foetal neurodevelopment.

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Chapter 6: General Conclusion

6.1 Implications of presented studies

This thesis aimed to further elucidate the specific effects of the *BDNF* and *COMT* genes on cognitive phenotypes, exploring the conditions under which neurogenetic effects are manifest. The impact of variables such as sex, personality traits and environmental stressors on the route from gene to cognitive phenotype were considered and novel effects were reported.

6.1.1 Relationship between *BDNF* and memory

The *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms have been inconsistently associated with memory performance (Barnett et al., 2008; de Frias et al., 2004; Kambeitz et al., 2012; Raz et al., 2009; van Wingen et al., 2010). The genetic underpinnings of memory performance are likely to vary between neurologically distinct forms of memory. Recall and recognition are forms of memory that may affected by different genes. The first study of this thesis (Chapter 2) sought to determine whether the *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms differentially influence performance on recall and recognition tasks, and whether they interact to affect performance on either task. The study was novel in its aim to examine whether these genes, alone or in interaction, have differential effects on recall and recognition in a single sample of young adults. The study demonstrated an effect of the *BDNF* val^{66}met polymorphism that is specific to recall, a form of memory particularly dependent on the hippocampus. Discovering gene and molecular pathways for hippocampal-dependent memory is an important step in the discovery of drug treatments for conditions in which memory is impaired (Papassotiropoulos & de Quervain, 2011). Candidate gene studies require well-described phenotypes with established biological substrates (Goldberg &

Weinberger, 2004) and this study provides evidence that distinguishing between recall and familiarity-based recognition is important when selecting potential genotype-phenotype combinations for research.

It should be noted that when the analysis from the first study was repeated with an additional 42 participants added (following data collection for the related study in Chapter 3, the participant sample of which was overlapping with that examined in Chapter 2), the effects of *BDNF* genotype on recall became stronger and a dose effect emerged (Appendix B.5), suggesting that the main effect of *BDNF* reported in Chapter 2 was not a false positive. In this repeated analysis, the interaction between *BDNF* and *COMT* became weaker (Tables B5.3 and B5.4). A main effect of *COMT* on recall, but not recognition, emerged when *COMT* genotype was tested at three levels (Table B5.4).

This thesis also contributes to accumulating research on the protective effects of Conscientiousness for recall performance. Conscientiousness has been demonstrated to have neuroprotective effects in older adults (e.g., Chapman et al., 2012; Hock et al., 2014; Wilson et al., 2015) and the study presented in Chapter 4 aimed to determine whether Conscientiousness moderates the previously documented effect of the *BDNF* val^{66}met polymorphism on recall performance in a sample of young adults. The study offers the first demonstration of Conscientiousness affecting the impact of the *BDNF* polymorphism on memory. This moderation suggests that environmental experiences conferred by having a conscientious personality can compensate for the genetic memory advantage associated with the *BDNF* met allele, widening the scope of the effects of Conscientiousness. Previous studies of the protective effects of Conscientiousness have focused solely on the deficits associated with aging (e.g., Hock et al., 2014; Martin et al., 2009; Wilson et al., 2015).

6.1.2 *COMT* Rs4680

The *COMT* val^{158}met polymorphism did not affect recall or recognition performance in the main analysis for the first study (Chapter 2, although see Table B5.4). As there is accumulating evidence suggesting that effects of the *COMT* gene differ between sexes, the study presented in Chapter 3 aimed to determine whether the *COMT* val^{158}met polymorphism has sex-specific effects on recognition performance that may be obscured in studies that do not consider gene-sex interactions. Face recognition is a form of cognition for which a female advantage is often reported (Herlitz & Lovén, 2013). The *COMT* val^{158}met was demonstrated to interact with sex to affect performance on face recognition memory. *COMT* genotype was only consequential for recognition memory in male participants, thus extending previous research on sex-specific effects of *COMT* on psychological phenotypes (e.g., Chen et al., 2011; Harrison & Tunbridge, 2008; O'Hara et al., 2006) to familiarity-based recognition of faces. It also provides the first demonstration of the well-documented sex difference in face recognition ability being specific to val homozygotes, a finding which suggests that interactions between oestrogens and the COMT enzyme may contribute to sex differences that have been noted in face recognition memory (e.g., Herlitz & Lovén, 2013). Sex-specific effects of the *COMT* val^{158}met polymorphism have tended to be noted in traits or phenotypes where sex differences have been traditionally observed.

6.1.3 *COMT* Rs165599

The most robust evidence of *COMT* variation affecting cognition comes from studies examining the effect of the *COMT* Rs4680 SNP on IQ (Barnett et al., 2008). The *COMT* gene has also been implicated in stress sensitivity (Walder et al., 2010). Consequently, the study presented in Chapter 5 aimed to determine whether potential effects of antenatal maternal stress on childhood IQ differ between *COMT* Rs165599 or Rs4680 genotypes. Results from

the ABC research implicated Rs165599, a relatively under-researched *COMT* SNP, in the relationship between antenatal maternal stress exposure and childhood cognitive ability. This is thought to be the first study to report a gene-environment interaction between Rs165599 and an environmental stressor on a cognitive phenotype. The present research also further establishes the need to consider the effects of *COMT* variants other than the val^{158}met polymorphism. The *COMT* val158met polymorphism has been the sole focus of many studies on the *COMT* gene and cognition. Further research on is needed the Rs165599 polymorphism and susceptibility to detrimental outcomes following stress exposure, determining the range of environments the effect occurs across and the duration of effects.

6.1.4 Inconsistencies in existing literature

This thesis indicates some of the factors that are likely to have contributed to inconsistent findings concerning the effects of the *BDNF* val^{66}met and *COMT* val^{158}met on cognitive outcomes. Sex-specific effects of the *COMT* gene and potential gene-environment interactions involving the *BDNF* gene could obscure gene-cognition relationships in studies not accounting for these factors. Similarly, studies collapsing across neurologically distinct forms of memory might underestimate or fail to detect genetic effects that are specific to a particular form.

6.2 Limitations of presented studies

6.2.1 Sample size

A general limitation of the research presented in this thesis is that the sample sizes are smaller than would be ideal. There is growing acknowledgement that candidate gene studies using small samples often do not replicate successfully (Chabris et al., 2012). Estimates of

effect size in smaller studies may be inflated, the so-called "winner's curse" (Button et al., 2013). Consequently, studies attempting to replicate studies with statistical significance values in the range of p ~ .05 may fail even when their samples sizes are comparable to those of the initial studies. Further research may reveal that true effect sizes are smaller than originally reported (Button et al., 2013). This demonstrates the importance of replication studies for converging on accurate estimates of effect, as well as the need for meta-analyses. There is also the related possibility that effects reported in this thesis are false alarms, again supporting the need for successful replication (Duncan & Keller, 2011).

Due to our small sample sizes, our studies may have been underpowered. Observed power estimates for reported effects ranged between ~50% and ~95%, while 80% is the usual standard for power. Lack of power appears to be a widespread issue in neuroscience (Button et al., 2013). Part of the problem may be that study sample sizes have not tended to increase over time, while the effects that are being searched for have become increasingly subtle – the low-hanging fruit have already been targeted (Button et al., 2013). Furthermore, given the highly polygenic nature of complex traits, effects in cognitive neurogenetics are likely to be particularly small and thus require larger samples for their detection. For example, Barnett and colleagues (2008) reported that the effect of *COMT* on IQ was d = .06 (equivalent to .1% of the total phenotypic variance). A larger sample would have provided greater power to detect subtle effects and increased confidence in the accuracy of our results.

6.2.2 Generalisability of findings

Participants in the current research were either young adults (Studies 1-3) or children (Study 4). This may be of consequence in that different, perhaps stronger, effects of the *BDNF* and *COMT* genes may occur in older individuals. For example, the *COMT* val^{158}met polymorphism is associated with prefrontal white matter integrity in older adults while there

were no reliable associations for adults nearer middle-age (Papenberg, Lövden, et al., 2015). Similarly, the *BDNF* val^{66}met polymorphism has a greater impact on hippocampal volumes after the age of 65 (Sanchez et al., 2011), consistent with the notion that genetic variation may be influential for brain maintenance in later life (Nyberg, Lövden, Riklund, Lindenberger, & Bäckman, 2012). As well as neuroanatomy, *COMT* and *BDNF* polymorphisms appear to be of greater consequence for cognitive abilities in older individuals than in young adults (Papenberg, Lindenberger, et al., 2015). Of particular relevance to the reported *COMT*-sex interaction, it has been reported that effects of *COMT* on cognition are sexually dimorphic only up until menopause (Papaleo, Sannino, Piras, & Spalletta, 2015). Generalisability of the current research is thus limited to the age groups sampled.

As our adult participants were individuals pursuing tertiary education in a wealthy nation, their backgrounds are likely to be relatively affluent. Our sample may be considered as being generally Western, educated, industrialised, rich and democratic (WEIRD; Henrich, Heine, & Norenzayan, 2010), outliers of wider humanity. This is relevant in that effects of genes on attained abilities are potentially greater for those who have more opportunities in life than for individuals more limited by environmental factors (Tucker-Drob et al., 2013).

The current research on young adults did not control for ethnicity and our participants came from a range of ethnic backgrounds. Although the *BDNF* met allele is present in lower frequencies in Caucasian populations than it is in Asian populations (Shimizu et al., 2004), research has tended to look at samples of European descent and data on potential ethnic differences is limited (Mandelman & Grigorenko, 2012). Further research on non-European samples is warranted and would assist in establishing whether BDNF effects vary between ethnicities. In regard to the *COMT* polymorphism, ethnicity appears to be a relevant factor to

consider when researching effects on psychological phenotypes (e.g., Wang et al., 2016). There is some indication that the met allele of COMT val158met may benefit cognitive function in European populations (e.g., Aguilera et al., 2008; Bruder et al., 2005) while the val allele is beneficial for those of East Asian descent (e.g., Wang et al., 2013; Yeh, Chang, Hu, Yeh, & Lin, 2009). These results highlight the need for future large sample gene-cognition studies that can adequately consider multiple potentially influential variables.

6.2.3 Mechanisms underlying effects

The presented research describes relationships, often conditional, between genes and cognitive abilities. Likely explanations for these relationships are posited on the basis of known effects of *COMT* and *BDNF*, as well as additional variables, on brain structure and function. No conclusive statements about the biological mechanisms underlying the demonstrated relationships can be made on the basis of these presented studies alone. For example, catecholamines other than dopamine may be contributing the effects of *COMT* variants on cognition. Uncertain mechanisms is a general limitation of behavioural genetics. Animal experiments and imaging designs can facilitate triangulation and give further confidence in proposed mechanisms.

6.2.4 Dissecting cognitive phenotypes

The presented research demonstrates the importance of distinguishing between recall and familiarity-based recognition when investigating the effects of genes on memory. These forms of memory can potentially be broken down further, with unique genetic contributions to different elements. Memory for previously experienced objects, for example, may involve different neural substrates than the familiarity-based recognition of faces (e.g., Calkins, Gur, Ragland, & Gur, 2005; Rimmele, Hediger, Heinrichs, & Klaver, 2009). It is consequently uncertain how specific the reported gene-cognition relationships are to the tasks used.

A further limitation stems from the possibility that memory tasks tap multiple cognitive phenotypes. Unrelated phenotypes such as general cognitive ability, attention, concentration, motivation, and working memory capacity could be affecting reported associations between genes and memory abilities (Papassotiropoulos & de Quervain, 2011). These phenotypes such as these could affect performance on the recall and recognition measures used in this research and were not controlled for.

6.3 Contributions from alternative study designs

6.3.1 Genome-wide association studies

Like candidate gene studies, genome-wide association (GWA) studies have sought to determine the specific genes that contribute to the heritability of cognitive abilities. GWA studies differ from candidate gene studies in that they take an atheoretical approach, using DNA microarrays to assess associations between a particular trait and potentially over one million DNA markers (Plomin, 2013). These markers, generally SNPs, are spread throughout most of the genome.

GWA studies have successfully identified associations between SNPs and a range of traits and disorders (Visscher, Brown, McCarthy, & Yang, 2012). Early GWA studies of general cognitive ability (e.g., Davies et al., 2011; Davis et al., 2010) found that, alone, the associations with the greatest effects explain no more than approximately 0.1% of the variance in ability. These suggest that the heritability of cognitive ability is highly polygenic, the result of many genes each with only a very small effect and the individual effects thus difficult to detect (Plomin, 2013; Plomin et al., 2016). These small individual effects are likely have contributed to the difficulty in replicating effects of specific genes on cognitive

abilities and support the need for large samples in gene-cognition research. Results from the GWA research have been taken to suggest that twin and adoption studies may have produced over-estimations of heritability (Plomin, Haworth, Meaburn, Price, & Davis, 2013).

GWA studies may reveal candidate genes not previously considered, thus complementing candidate gene research (Papassotiropoulos & de Quervain, 2011). The greater risk of Type I errors in genome-wide studies further increases the need for replication of effects. Type II errors may similarly be an issue; GWA studies require large samples in order for *p*-values to withstand corrections for multiple comparisons (Potkin et al., 2009). Like candidate gene studies, GWA studies have not invariably yielded replicable results (Potkin et al., 2009); no single SNP has been consistently associated with IQ in GWA studies (Kirkpatrick, McGue, Iacono, Miller, & Basu, 2014). GWA studies generally treat SNPs as single fixed effects, which limits their utility (Korte & Farlow, 2013; Wang, Murk, & DeWan, 2015). The genome-wide gene-by-environment interaction approach, while still in its early days, may prove useful in harnessing the strengths of the GWA approach to instead investigate gene-environment interactions (Wang et al., 2015).

6.3.2 Genome-wide complex trait analysis

Genome-wide complex trait analysis (GCTA; Yang, Lee, Goddard, & Visscher, 2011) is a particularly recent design in gene research. This technique uses hundreds of thousands of SNPs to generate an estimate of similarity in the DNA of each pair of individuals in a large, genetically unrelated sample. This chance genetic similarity is then related to phenotypic similarity between the individuals. This technique requires a sample size in the thousands (Vinkhuyzen, Wray, Yang, Goddard, & Visscher, 2013), but has produced evidence for cognitive abilities being influenced considerably by genes in children (e.g., Benyamin et al., 2014; Robinson et al., 2015; St Pourcain et al., 2014) and adults (e.g., Davis et al., 2015).

The results of these studies are not inconsistent with the heritability estimates generated from twin and adoption research, suggesting a narrowing of the "missing heritability" gap (Plomin & Deary, 2015; Plomin et al., 2016). GCTA studies further demonstrate the strongly polygenic nature of cognitive abilities and thus the need to consider the combined effects of multiple genes on cognitive phenotypes.

6.4 Future Directions

6.4.1 Imaging genetics

Imaging genetics studies have tended to produce effects of a larger size than those of behavioural genetics studies, perhaps due to them measuring phenotypes that are more proximate to the effects of SNPs on the gene products (Papassotiropoulos & de Quervain, 2011). It could also be more difficult for individuals to behaviourally compensate for genetically affected neurophysiological differences (Goldberg & Weinberger, 2004). Compensation efforts may obscure genotype effects at the behavioural level that may be revealed during neuroimaging. Imaging studies may thus have a greater sensitivity to differences between genetic variants than behavioural studies and require smaller sample sizes.

Imaging genetics research can be used to further substantiate relationships shown in behavioural genetics (and vice versa), potentially offering information about the underlying mechanisms. For example, future research could seek to examine whether Conscientiousness moderates the relationship between *BDNF* genotype and LTP in the same manner that it moderates the relationship between *BDNF* genotype and recall in Chapter 4. LTP-like phenomena can now be assessed non-invasively in humans (see Lamb et al., 2014 for a

review). One method involves the use of electroencephalography (EEG) and repetitive visual stimulation (e.g., Teyler et al., 2005). This involves the measurement of visual-evoked potentials (VEPs) in response to a checkerboard stimulus. For a baseline measurement, this stimulus is presented at a low frequency of 1 Hz. In the 'tetanus' phase, the stimulus is then presented at a relatively high frequency. It is then presented at baseline frequency again, during which a post-tetanus measurement is taken. Teyler and colleagues (2005) have demonstrated that the tetanic presentation results in the N1b component of the VEP being selectively altered, with higher amplitudes following the tetanus. This is thought to constitute LTP-like plasticity and similar effects have been shown in a replication using fMRI (Clapp et al., 2005). Another method for measuring LTP-like effects uses repetitive transcranial magnetic stimulation (rTMSl; e.g., Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005), although it is not clear whether rTMS-induced changes have the input-specificity shown in animal studies of LTP.

Demonstrating that Conscientiousness moderates the relationship between *BDNF* genotype and LTP-like synaptic plasticity would enable further substantiation of plausible routes through which our demonstrated moderation could occur. It should be noted that, as is the case with behavioural genetics research, data from imaging studies will still only be correlational and causal relationships cannot be assumed (Papassotiropoulos & de Quervain, 2011); altering levels of BDNF and the COMT enzyme would be required in order to progress towards causal inferences.

6.4.2 Epigenetic mechanisms

Further research into the effects of environment and lifestyle on gene expression could complement research into gene-environment interactions on cognitive ability. As monozygotic twins age, their patterns of DNA methylation becomes increasingly discordant

(Talens et al., 2012). This indicates environmental regulation of gene expression over the course of the lifespan. The emergent sub-discipline of neuroepigenetics research has rendered the nature versus nurture debate irrelevant as the biochemical interplay between our genes and experiences has been further elucidated (Sweatt, 2009; 2013).

Epigenetic mechanisms of the central nervous system have been implicated in learned behaviour and neuroplasticity (Day & Sweatt, 2011), as well as a range of disorders (Petronis, 2010). For practical reasons, most research into epigenetic mechanisms has been done on animals (Sweatt, 2013). Longitudinal data showing that experiences and lifestyles impact gene expression (and that this gene expression, in turn, has consequences for brain function and cognitive performance) could support the hypothesis that epigenetic mechanisms drive the noted gene-environment interactions (Papenberg, Lindenberger, et al., 2015). In mice, exposure to prenatal adversity has been shown to alter methylation of the *BDNF* gene in the hippocampus (Kundakovic et al., 2014). Analysing both genetic and epigenetic variation in humans can be helpful in studying the route through which *BDNF* and *COMT* influence cognitive phenotypes (e.g., van der Knaap et al., 2014). It is, however, important to acknowledge that gene-environment interactions might also occur in the absence of any epigenetic modifications (Papenberg, Lindenberger, et al., 2015).

6.5 Conclusion

In conclusion, this thesis builds upon research on the effects of the *BDNF* val^{66}met and *COMT* val^{158}met polymorphisms on memory and the effects of *COMT* variants on general intelligence. The *BDNF* val^{66}met polymorphism was shown to impact recall performance in young adults, while not affecting familiarity-based recognition. This indicates the importance of distinguishing between these forms of memory in gene-cognition research.

Conscientiousness moderates this relationship between the *BDNF* polymorphism and recall, perhaps through its role in predicting neuroprotective health-related behaviours. The *COMT* val^{158}met interacts with sex to affect the familiarity-based recognition of faces in young adults, while the under-researched *COMT* Rs165599 SNP interacts with exposure to antenatal maternal stress to affect performance on an IQ measure during childhood. Future research on gene-cognition relationships requires samples that are large enough to enable thorough examination of gene-gene and gene-environment interactions, as well as consideration of relevant variables such as sex and age. Gene effects are typically small and may be evident in one context while being inconsequential in another. Converging evidence from multiple lines of research should be incorporated into theories concerning gene-cognition relationships and the biological processes that underlie them.

Appendix A: Assumption Testing for Statistical Analyses

A.1 Study One (Chapter 2)

The data were screened for MANOVA assumptions. Normality tests were carried out on each dependent variable (Faces scores and Family Pictures scores) at each level of the independent variables (*BDNF* genotype and *COMT* genotype). For the *BDNF* val homozygotes, Faces scores violated normality according to the Kolmogorov-Smirnov test ($KS_{(53)} = .164$, $p = .001$). Faces scores were normally distributed for *BDNF* met allele carriers and Family Pictures scores were normally distributed for both levels of *BDNF* genotype ($p > .05$ for Kolmogorov-Smirnov tests). For *COMT* val allele carriers, Faces scores violated normality according to the Kolmogorov-Smirnov test ($KS_{(72)} = .129$, $p = .004$). Faces scores were normally distributed for the *COMT* met homozygotes and Family Pictures scores were normally distributed for both levels of *COMT* genotype ($p > .05$ for Kolmogorov-Smirnov tests). No influential univariate outliers were present. As all skewness and kurtosis values were in the range of -1 to +1 (Table A1), data were considered acceptable for parametric procedures.

Due to small cell sizes, Shapiro-Wilk tests were used to evaluate normality for *BDNF-COMT* genotype combinations. For *BDNF-COMT* genotype combinations, Family Pictures scores were consistent with the assumption of normality ($p > .05$ for Shapiro-Wilk tests). Faces scores for *BDNF* val homozygotes with the *COMT* val allele violated normality according to the Shapiro-Wilk test ($SW_{(40)} = .936$, $p = .025$), although skewness and kurtosis values were in the acceptable range of -1 to +1. Faces scores for other *BDNF-COMT* genotype combinations were normally distributed ($p > .05$ for Shapiro-Wilk tests). No influential multivariate outliers were present.

Table A1

Skewness and Kurtosis Statistics for Faces and Family Pictures Scores at Each Level of BDNF and COMT.

Memory Test	Gene	Genotype	Skewness		Kurtosis	
			Statistic	Std Error	Statistic	Std Error
Faces	BDNF	Val/Val	-.942	.33	.808	.64
		Met allele	-.459	.35	-.248	.68
	COMT	Val allele	-.566	.28	-.292	.56
		Met/Met	-.076	.44	-.484	.86
Family Pictures	BDNF	Val/Val	-.829	.33	.988	.64
		Met allele	-.559	.35	-.321	.68
	COMT	Val allele	-.783	.28	.533	.56
		Met/Met	-.693	.44	-.198	.86

While the Levene's test for homogeneity of variance was significant for both Faces ($F_{(3,96)} = 3.819$, $p = .012$) and Family Pictures ($F_{(3, 96)} = 3.819$, $p = .021$), convention suggests the assumption of homogeneity is met if the largest standard deviation is no more than twice the smallest standard deviation. The greatest difference in standard deviation was between

COMT val allele carriers (*SD* = 12.0) and met homozygotes (*SD* = 6.5) for Faces scores, within the role of thumb. As detailed by Nimon (2012), the Box's M test was used to determine whether the multivariate extension of the homogeneity of variance assumption was met. Due to the high sensitivity of the Box M test (Tabacknick & Fidell, 2001), Nimon (2012) suggests that if the Box M test is significant at $p < .001$ and sample sizes are unequal, the assumption is violated. In the present analysis, the Box M test was not significant at this level ($p > .001$) indicating the assumption was met. Multicollinearity was not present, with Faces and Family Pictures scores showing a weak relationship ($r = .215$). A linear relationship was observed for each cell.

A.2 Study Two (Chapter 3)

The data were screened for ANOVA assumptions. Normality tests were carried out on the dependent variable (Faces scores) at each level of the independent variables (*COMT* genotype and sex). Kolmogorov-Smirnov tests were non-significant ($p > .05$) at each level of *COMT* genotype, indicating normality. While the Kolmogorov-Smirnov test for the scores of males was non-significant ($p > .05$), the test was significant for females ($KS_{(90)} = .101$, $p = .025$). Skewness and Kurtosis values are presented in Table A2. As skewness and kurtosis values for female scores were well within in the range of -1 to +1, data were considered acceptable for parametric procedures. No influential outliers were present in the dataset.

Due to small cell sizes, Shapiro-Wilk tests were used to evaluate normality for *COMT*-Sex combinations. For all *COMT*-Sex combinations, Faces scores were consistent with the assumption of normality ($p > .05$ for Shapiro-Wilk tests). No influential outliers were present.

Table A2

Skewness and Kurtosis Statistics for Faces at Each Level of COMT and Sex.

Memory Test	Independent Variable	Level	Skewness		Kurtosis	
			Statistic	Std Error	Statistic	Std Error
Faces	COMT	Val/Val	-.356	.38	-.014	.75
		Val/Met	-.443	.29	-.431	.57
		Met/Met	-.240	.40	-.568	.78
	Sex	Male	-.438	.33	.158	.65
		Female	-.411	.25	-.522	.50

The Levene's test was not significant ($F_{(5,136)} = 1.455$, $p = .209$), indicating that the assumption of homogeneity of variance holds.

A.3 Study Three (Chapter 4)

Linearity of the collective and individual independent variables was established via visual inspection of a scatterplot plotting studentised residuals against unstandardized predicted values, as well as partial regression plots. These plots also showed no evidence of heteroscedasticity. No influential outliers were present, with the largest Cook's distance value

in the dataset being 0.2. The assumption of independence of residuals was met, with the Durbin-Watson statistic indicating an absence of autocorrelation of residuals (d = 1.819). Residuals also approximated a normal distribution, as indicated by a non-significant Kolmogorov-Smirnov test ($KS_{(102)}$ = .074, p = .192).

There was no significant relationship between BDNF genotype and Conscientiousness ($r_{(140)}$ = -.055, p > .05). The continuous predictor variables were centred to avoid the problem of multicollinearity and tests for multicollinearity indicated that a low level of multicollinearity was present (VIF values < 2). Consequently, assumption testing supported data being appropriate for parametric procedures.

A.4 Study Four (Chapter 5)

A.4.1 Normality for ANOVA with Rs4680

Normality of residual FSIQ scores was assessed at each level of *COMT* Rs4680 and antenatal maternal stress, including all genotype-stress combinations. For both ages 7 and 11, the normality assumption was satisfied for each cell (p > .05 for Kolmogorov-Smirnov tests). Cook's distance values were examined and no influential outliers were identified.

A.4.2 Normality for ANOVA with Rs165599

Normality of residual FSIQ scores was assessed at each level of *COMT* Rs165599 and antenatal maternal stress, including all genotype-stress combinations. For both ages 7 and 11, the normality assumption was satisfied for each cell (p > .05 for Kolmogorov-Smirnov tests). Cook's distance values were examined and no influential outliers were identified.

These assumptions of normality and absence of outliers were likewise fulfilled for each cell when antenatal maternal stress was substituted for either maternal stress at age 3.5 years or maternal stress at 7 years.

A.4.3 Homogeneity of variance

For the analysis including *COMT* Rs4680 and antenatal maternal stress, the Levene's test was not significant for IQ at age 7 ($F_{(3,404)} = 1.267$, $p = .285$) or age 11 ($F_{(3,404)} = .605$, $p = .612$). For the analysis including *COMT* Rs165599 and antenatal maternal stress, the Levene's test was not significant for IQ at age 7 ($F_{(3,467)} = .286$, $p = .835$) or age 11 ($F_{(3,467)} = .185$, $p = .907$). Levene's tests were also non-significant when antenatal maternal stress was substituted for either maternal stress at 3.5 years or maternal stress at 7 years ($p > .05$). Similarly, the Box's M test of equality of covariance matrices was not significant for any analysis ($p > .05$). These results indicate that the assumption of homogeneity of variance holds.

Appendix B: Additional Analyses

B.1 Study One (Chapter 2)

Table B1.1

Mean Recall Scores for BDNF and COMT Genotypes

BDNF	*COMT*	Mean	Std. Error	*N*
Val/Val	Val/Val	75.4	3.43	15
	Val/Met	77.7	2.65	25
	Met/Met	81.8	3.68	13
	Total	78.3	1.90	53
Val/Met	Val/Val	75.7	5.02	7
	Val/Met	73.4	3.32	16
	Met/Met	70.0	3.55	14
	Total	73.0	2.33	37
Met/Met	Val/Val	75.9	5.94	5
	Val/Met	81.3	6.64	4
	Met/Met	51.6	13.27	1
	Total	69.6	5.33	10
Total	Val/Val	75.7	2.83	27
	Val/Met	77.5	2.63	45
	Met/Met	67.8	4.74	28
	Total	75.8	1.34	100

Table B1.2

Mean Recognition Scores for BDNF and COMT Genotypes

BDNF	*COMT*	Mean	Std. Error	*N*
Val/Val	Val/Val	78.6	2.79	15
	Val/Met	79.3	2.16	25
	Met/Met	81.1	2.99	13
	Total	79.7	1.54	53
Val/Met	Val/Val	86.0	4.08	7
	Val/Met	78.9	2.70	16
	Met/Met	82.7	2.88	14
	Total	82.6	1.89	37
Met/Met	Val/Val	73.3	4.83	5
	Val/Met	72.4	5.40	4
	Met/Met	81.3	10.79	1
	Total	75.7	4.33	10
Total	Val/Val	79.3	2.30	27
	Val/Met	76.9	2.14	45
	Met/Met	81.7	3.85	28
	Total	79.8	1.08	100

Table B1.3

MANOVA for Recall (Family Pictures) and Recognition (Faces) Scores with BDNF Genotype and COMT Genotype as the Between-Subjects Variables

Source		*F*	df	*p*
BDNF Genotype[a]	Recall	3.522	1	.064
	Recognition	.082	1	.775
COMT Genotype[b]	Recall	.060	2	.942
	Recognition	.829	2	.440
*BDNF*COMT*	Recall	2.008	2	.140
	Recognition	.330	2	.720
Error			94	

[a] *BDNF* genotype at two levels (val/val and met allele)

[b] *COMT* genotype at three levels (val/val, val/met, met/met)

Table B1.4

MANOVA for Recall (Family Pictures) and Recognition (Faces) Scores with BDNF Genotype and COMT Genotype as the Between-Subjects Variables

Source		*F*	df	*p*
BDNF Genotype[a]	Recall	1.598	2	.208
	Recognition	.694	2	.502
COMT Genotype[b]	Recall	.060	2	.942
	Recognition	.829	2	.440
*BDNF*COMT*	Recall	1.623	4	.175
	Recognition	.515	4	.725
Error			91	

[a] *BDNF* genotype at three levels (val/val, val/met, met/met)

[b] *COMT* genotype at three levels (val/val, val/met, met/met)

B.2 Study Two (Chapter 3)

Table B2.1

Mean Recognition Scores by Sex and COMT Genotype

Sex	*COMT*	Mean	Std. Error	*N*
Male	Val allele	75.4	1.51	41
	Met/Met	86.6	2.91	11
	Total	81.0	1.64	52
Female	Val allele	81.5	1.19	66
	Met/Met	79.9	1.97	24
	Total	80.7	1.15	90
Total	Val allele	78.5	0.96	107
	Met/Met	83.2	1.76	35
	Total	79.9	0.85	142

Table B2.2

Two-way ANOVA for Face Recognition Scores with COMT Genotype and Sex as the Between-Subjects Variables

Source	*F*	df	*p*
Sex	.023	1	.880
COMT Genotype[a]	5.653*	1	.019
*COMT**Sex	10.203**	1	.002
Error		138	

*$p < .05$, ** $p < .01$

[a] *COMT* genotype at two levels (val allele and met/met)

B.3 Study Three (Chapter 4)

Table B3

Results of Hierarchical Regression Analysis for Variables Predicting Recall Performance

	Step 1			Step 2		
Variable	*B*	*SE B*	β	*B*	*SE B*	β
BDNF Genotype[a]	-3.585	2.586	-.136	-3.600	2.553	-.136
Conscientiousness	.100	.054	.183	.009	.072	.016
Genotype x Conscientiousness				.201	.106	.247†
R^2		.055			.088	
F for ΔR^2		2.877			3.590†	

†p = .061

[a] *BDNF* genotype at two levels (val/val and met allele)

B.4 Study Four (Chapter 5)

Table B4.1

Mean Full-Scale IQ Scores for Ages 7 and 11 Years at Each Level of Rs165599 Genotype.

Independent Variable	Level	*N*	Age			
			7 Years		11 Years	
			Mean	Std. Dev	Mean	Std. Dev
Rs165599	G/G	40	110.4	13.20	112.7	14.07
	G/A	208	110.1	13.51	110.5	13.13
	A/A	223	110.1	13.57	110.1	13.77

Table B4.2

Omnibus Split-Plot ANOVA for IQ Scores with Rs165599 Genotype and Antenatal Maternal Stress as the Between-Subjects Variables, Birthweight for Gestational Age as a Covariate, and Age as the Within-Subjects Variable.

Source	*F*	df	*p*
Age	4.244*	1	.040
Rs165599	.250	2	.779
Antenatal Stress	9.024**	1	.003
Birthweight for Gestation	4.957*	1	.026
Age*Rs165599	1.622	2	.199
Age*Antenatal Stress	2.867	1	.091
Age*Birthweight for Gestation	3.339	1	.068
Rs165599*Antenatal Stress	2.083	1	.126
Age*Antenatal Stress*Rs165599	3.795*	2	.023
Error		464	

*$p < .05$, **$p < .01$

[a] Rs165599 genotype at three levels (G/G, G/A, A/A)

Table B4.3

Results of Hierarchical Regression Analysis for Variables Predicting IQ at Age 7

	Step 1			Step 2		
Variable	*B*	*SE B*	β	*B*	*SE B*	β
Rs165599[a]	-.343	.976	-.016	.088	.999	.004
Antenatal Stress	-.190	.094	-.093*	-.285	.106	-.140**
Birthweight for Gestational Age	-1.767	1.269	-.065	-1.622	1.268	-.059
Rs165599 x Antenatal Stress				.264	.137	.102†
R^2		.014			.022	
F for ΔR^2		2.243			2.617†	

† $p = .055$, *$p = .044$, **$p = .007$

[a] Rs165599 genotype at three levels (G/G, G/A, A/A)

Table B4.4

Results of Hierarchical Regression Analysis for Variables Predicting IQ at Age 11

	Step 1			Step 2		
Variable	*B*	*SE B*	β	*B*	*SE B*	β
Rs165599[a]	-1.547	.933	-.071	-1.389	.957	-.064
Antenatal Stress	-.261	.089	-.127**	-.299	.102	-.145*
Birthweight for Gestational Age	-3.713	1.198	-.134***	-3.665	1.200	-.133***
Rs165599 x Antenatal Stress				.099	.132	.038
R^2		.041			.042	
F for ΔR^2		7.566‡			.560	

* $p = .004$, **$p = .003$, ***$p = .002$, ‡$p < .001$

[a] Rs165599 genotype at three levels (G/G, G/A, A/A)

B.5 Study One (Updated Analyses)

Table B5.1

Mean Recall Scores for BDNF and COMT Genotypes

BDNF	*COMT*	Mean	Std. Error	*N*
Val/Val	Val/Val	74.8	2.77	22
	Val/Met	79.8	2.19	35
	Met/Met	79.1	3.35	15
	Total	77.9	1.62	72
Val/Met	Val/Val	73.0	4.10	10
	Val/Met	75.4	2.45	28
	Met/Met	68.9	2.98	19
	Total	72.4	1.88	57
Met/Met	Val/Val	68.8	5.30	6
	Val/Met	81.0	5.30	6
	Met/Met	51.6	13.00	1
	Total	67.1	4.99	13
Total	Val/Val	72.2	2.42	38
	Val/Met	78.7	2.08	69
	Met/Met	66.5	4.58	35
	Total	75.5	1.12	142

Table B5.2

Mean Recognition Scores for BDNF and COMT Genotypes

BDNF	*COMT*	Mean	Std. Error	*N*
Val/Val	Val/Val	77.8	2.14	22
	Val/Met	80.9	1.70	35
	Met/Met	81.1	2.59	15
	Total	79.9	1.26	72
Val/Met	Val/Val	83.1	3.17	10
	Val/Met	79.1	1.90	28
	Met/Met	82.7	2.30	19
	Total	81.6	1.45	57
Met/Met	Val/Val	73.3	4.10	6
	Val/Met	73.6	4.10	6
	Met/Met	81.3	10.04	1
	Total	76.0	3.86	13
Total	Val/Val	78.1	1.87	38
	Val/Met	77.9	1.61	69
	Met/Met	81.7	3.54	35
	Total	79.9	.85	142

Table B5.3

MANOVA for Recall (Family Pictures) and Recognition (Faces) Scores with BDNF Genotype and COMT Genotype as the Between-Subjects Variables

Source		*F*	df	*p*
BDNF Genotype[a]	Recall	7.580	1	.007
	Recognition	.007	1	.934
COMT Genotype[b]	Recall	1.165	1	.282
	Recognition	1.903	1	.170
*BDNF*COMT*	Recall	2.383	1	.125
	Recognition	.449	1	.504
Error			138	

[a] *BDNF* genotype at two levels (val/val and met allele)

[b] *COMT* genotype at two levels (val allele and met/met)

Table B5.4

MANOVA for Recall (Family Pictures) and Recognition (Faces) Scores with BDNF Genotype and COMT Genotype as the Between-Subjects Variables

Source		*F*	df	*p*
BDNF Genotype[a]	Recall	3.776	2	.025[c]
	Recognition	1.062	2	.349
COMT Genotype[b]	Recall	4.010	2	.020[c]
	Recognition	.499	2	.608
*BDNF*COMT*	Recall	1.305	4	.271
	Recognition	.686	4	.603
Error			133	

[a] *BDNF* genotype at three levels (val/val, val/met, met/met)

[b] *COMT* genotype at three levels (val/val, val/met, met/met)

[c] Post-hoc tests with Bonferroni adjustments were performed on the significant main effects; no pairwise comparisons were statistically significant

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