The genetics of cognitive biases in the development of psychiatric disorders

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Statement of originality

I, John Paul Vincent, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below, and my contribution indicated. Previously published material is also acknowledged below. I attest that I have exercised reasonable care to ensure that the work is original and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material. I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis. I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university. The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

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Details of collaboration

The work presented in Chapters four and five of the current thesis was undertaken as part of the CogBIAS project, a large longitudinal study with multiple repeat measures of cognitive biases, life experiences as well as various subjective measures including depression and anxiety. Upon commencing my PhD, two waves of phenotypic data had been collected and DNA samples had been obtained from all CogBIAS project participants. I was responsible for the management and cleaning of all genetic data for analysis involved in Chapters four and five of the current thesis as well as for general use in the CogBIAS-L-S. I was also responsible for the curation of DNA samples whilst personally genotyping the entire CogBIAS sample (n=994) for the serotonin transporter polymorphism (5-HTTLPR) in the promoter region of the SLC6A4, used in Chapter four. This was done under the support and supervision of Dr Cathy Fernandes at the Social, Genetic and Developmental Psychiatry Centre at Kings College London. All other work presented in the current thesis, including all work towards the Cognition and Response to Environmental Stimulus (CRESt) study that formed the basis for Chapter Three, is to the best of my knowledge original work that I conducted throughout the course of my PhD.

Publications relevant to this thesis

Published

Assary, E., **Vincent, J**., Machlitt-Northen, S., Keers, R., & Pluess, M. (2020). The Role of Gene-Environment Interaction in Mental Health and Susceptibility to the Development of Psychiatric Disorders. In Beyond Our Genes (pp. 117-138). Springer, Cham.

Assary, E., **Vincent, J. P.,** Keers, R., & Pluess, M. (2018). Gene-environment interaction and psychiatric disorders: Review and future directions. *Seminars in Cell and Developmental Biology*, 77, 133-143. Academic Press.

Booth, C., Songco, A., Parsons, S., Heathcote, L., **Vincent, J**., Keers, R. and Fox, E., 2017. The CogBIAS longitudinal study protocol: Cognitive and genetic factors influencing psychological functioning in adolescence. *BMC Psychology*, 5(1), p.41.

Abstract

Evidence from largely independent lines of research suggests that genetic variation, environmental factors, and individual differences in cognitive biases are associated with risk for depression and anxiety. These independent lines of research, if combined, may advance our understanding of individual differences associated with such disorders. Therefore, examining genes, environments, gene-by-environment interactions, and cognitive biases associated with such affective disorders may provide further insight into their development. This thesis aimed to test this integrated theory, recently formulated in the CogBIAS hypothesis (Fox & Beevers, 2016), across three studies featuring two samples. The first sample included 74 adults, and the second sample 504 adolescents from the CogBIAS Longitudinal Study. In study one, primary data was used to assess the effects of cognitive biases on levels of affect in response to daily life events. In study two, the effects of both genes and the environment on the development of cognitive biases were assessed. In study three, the mediation of polygenic risk for major depression by cognitive biases on later anxiety and depression symptoms was explored. According to results, negative interpretation bias was significantly associated with negative perceptions of daily life events, and significantly moderated the effects of positive environmental contexts. Positive and negative life events and most candidate variants tested were associated with the development of memory and interpretation bias, with candidate variants also collectively and individually moderating the effect of life events. Finally, memory and interpretation bias were found to share genetic architecture with depression and mediate polygenic risk for major depression on later depression symptoms. Notwithstanding some statistical and methodological limitations, the current thesis provides support for elements of the CogBIAS hypothesis, whilst also suggesting that levels of positive cognitive biases may be of great importance to the development of affective disorders, and a potential target for future treatment and prevention.

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1. Chapter 1: Introduction – Examining Genetic and Environmental Influences on Depression, Anxiety and Cognitive Biases'

*N.B. This chapter contains information adapted for the following publications:

Assary, E., **Vincent, J. P**., Keers, R., & Pluess, M. (2018). Gene-environment interaction and psychiatric disorders: Review and future directions. In Seminars in cell & developmental biology (Vol. 77, pp. 133-143). Academic Press.

Assary, E., **Vincent, J**., Machlitt-Northen, S., Keers, R., & Pluess, M. (2020). The Role of Gene-Environment Interaction in Mental Health and Susceptibility to the Development of Psychiatric Disorders. In Beyond Our Genes (pp. 117-138). Springer, Cham.

One third of all disabilities worldwide can be accounted for by psychiatric disorders (World Health Organization, 2008). Of these major depression is amongst the most prevalent and debilitating (Kessler, Chiu, Demler, & Walters, 2005), and a major public health concern as it accounts for 40.5% of disability-adjusted life years (Whiteford et al., 2013). Associated with massive costs for both the individual and society, depression is the leading cause of disability the world over (World Health Organization, 2016). Similarly, anxiety disorders have been said to be amongst the world's most prevalent group of psychiatric disorders and, like depression (Kessler et al., 2009), responsible for a substantial health burden on society (World Health Organization, 2008). However, whilst the detrimental social and economic impact of psychiatric disorders, such as depression and anxiety, has been well established, adequate treatment strategies have not (Millan, Goodwin, Meyer-Lindenberg, & Ögren, 2015). Furthermore, whilst research has demonstrated that depression and anxiety can begin in childhood (Gregory et al., 2007), in many cases childhood onset of related symptoms often goes untreated for some time (Eley et al., 2008). Therefore, it is of great importance to understand the development of these highly prevalent disorders, as well as associated phenotypes, such as cognitive biases that could play an important role and provide new potential sites for novel treatments and interventions.

This chapter aims to provide a comprehensive review of literature relevant to the current thesis. Firstly, the aetiology of depression and anxiety will be discussed with a specific focus on quantitative genetic studies, before moving on to the effects of environmental factors. A review of relevant molecular genetic research, including candidate gene, genome-wide and gene-by-environment interaction (GxE) studies will follow before introducing cognitive theory of depression and anxiety and the effect of specific cognitive biases demonstrated through experimental research. The chapter will then bring together these often-separate lines of

research to highlight the shared genetic architecture between such affective disorders and cognitive biases and discuss cognitive biases as potential intermediate phenotypes and treatment targets for affective disorders. Lastly, the CogBIAS hypothesis will be presented before outlining the aims and hypotheses of the current thesis.

1.1. Aetiology of depression and anxiety

Both depression and anxiety are complex disorders and amongst the earliest to emerge with quantitative genetic studies suggesting that they are also both moderately heritable (Sullivan, Daly, & O'Donovan, 2012). Twin models represent an important first step to understanding the aetiology of such disorders as they allow for the exploration of variance explained by genes (the heritability) as well as shared and non-shared environment. For example, heritability estimates from twin studies have been demonstrated as ranging between 20-30% for depression (Sullivan, Neale, & Kendler, 2000) and 25-60% for anxiety (Franić, Middeldorp, Dolan, Ligthart, & Boomsma, 2010; Gregory & Eley, 2007; Hettema, Neale, & Kendler, 2001), with the remaining proportion being attributable to either shared or non-shared environmental factors in both cases.

For some time research has consistently demonstrated that both genetic and environmental risk factors have a significant impact on individual differences in both anxiety and depression symptoms in children (Boomsma, Van Beijsterveldt, & Hudziak, 2005; Edelbrock, Rende, Plomin, & Thompson, 1995; Eley & Stevenson, 1999; Rice, Harold, & Thapar, 2002; Topolski et al., 1997), adolescents (Eley & Stevenson, 1999; Rice et al., 2002; Thapar & McGuffin, 1994; Topolski et al., 1997), and adults (K. S. Kendler, Heath, Martin, & Eaves, 1986; Mackinnon, Henderson, & Andrews, 1990). For example, Kendler et al (1986) assessed the aetiology of 14 depression and anxiety symptoms in a sample of 3,798 adult twin pairs from the Australian National Health and Medical Research Council Twin Register. For the majority of symptoms, they demonstrated that genetic factors explained a significant proportion of the variance with heritability estimates ranging from 33-46%. The remaining variance were best explained by unique (non-shared) environmental effects specific to the individual. A later twin study by Eley and Stevenson (1999) has also shown similar effects in child and adolescent depression and anxiety across both males and females measured using the Children's Depression Inventory (CDI: (Maria Kovacs, 1981; M Kovacs, 1985)) and the Trait scale of the State-Trait Anxiety Inventory for Children (STAIC: (Spielberger & Edwards, 1973)). Here researcher assessed 490 twin pairs aged between 8-16 demonstrating genetic and

environmental influences on depression and anxiety as well as the extent to which they are shared between sexes in both childhood and adolescents. Univariate analysis showed genetic effect on depression and anxiety in childhood as ranging from 8-28% with shared and non-shared environmental effects ranging from 19-37% and 40-62% respectively. In adolescents these ranges of effect on depression and anxiety increased with genetic effects accounting for between 2-57%, and shared and non-shared environmental effects accounting for between 1-56% and 40-55% respectively. Bivariate genetic analyses also revealed that genetic effects on both depression and anxiety are shared across children and adolescents of both sexes.

In addition to these studies, several longitudinal twin studies have also demonstrated variations in both genetic and environmental influences overtime. For example, a considerable amount of research regarding many complex traits and disorders has shown that the heritability estimates are moderate to low in childhood and tend to increase over time into adulthood. This effect has been shown for behavioural traits such as intelligence quotient (IQ) (Bergen, Gardner, & Kendler, 2007) as well as for psychiatric disorders including depression (Bergen et al., 2007; Lau & Eley, 2006), and anxiety (Bergen et al., 2007) amongst others. In one such study, the depressive symptoms of 1820 adolescent twin and sibling pairs were assessed through self-report across three waves (Lau & Eley, 2006), demonstrating moderate genetic effects on depressive symptoms at each wave. Multivariate analysis also confirmed that stable genetic effects at wave 1, and new genetic effects at wave 2 contributed in part to the continuation of depressive symptoms. These findings were in keeping with similar previous research (O'Connor, Neiderhiser, Reiss, Hetherington, & Plomin, 1998; Scourfield et al., 2003; Silberg et al., 1999), suggesting that from adolescents to early adulthood genetic effects contribute essentially to the stability of depressive symptoms but also to their changes over time.

In a later study, the development of genetic effects on both depression and anxiety symptoms as ‘developmentally stable’ or ‘developmentally dynamic’ was assessed using self-report questionnaires in a Swedish population sample of over 2,000 twins across four timepoints from 8-20 years old (K. Kendler, Gardner, & Lichtenstein, 2008). Genetic effects had a strong impact on the depression and anxiety symptom scores reported by both parents and twin pairs with heritability estimates that ranged from 72% to 89%. In line with a dynamic developmental trajectory from childhood to early adulthood, there was evidence for novel genetic effects on depression and anxiety symptoms ‘coming online’ at timepoint two (13-14), three (16-17), and four (19-20) highlighting genetic innovation over time. Attenuation was also

observed as the genetic factors explaining 72% and 89% of the variance at timepoints one and two, respectively, dropped dramatically by timepoint four. The findings from this study, much like those from the previous study by Lau and Eley (2006), were in keeping with previous research (K. S. Kendler et al., 2008; Scourfield et al., 2003), further supporting the suggestion that whilst genes impacting on depression and anxiety symptoms change through development, the attenuation and innovation of genetic effects contribute to their continuation and stability over time. In further support of this notion, a recent study examining 2,619 twins and siblings, prospectively assessed for depression and four anxiety symptoms at mean ages of 15, 17, and 20, highlighted similar findings (Waszczuk, Zavos, Gregory, & Eley, 2016). Once again, the results supported broad and relatively stable genetic effects on symptoms of both depression and each of the four anxiety scales, with the emergence of new genetic factors (K. S. Kendler et al., 2008), and a decline through development of earlier genetic factors (Bartels et al., 2004; Haberstick, Schmitz, Young, & Hewitt, 2005; K. Kendler et al., 2008; K. S. Kendler et al., 2008; Lau & Eley, 2006; Lewis & Plomin, 2015; M. Nivard et al., 2015; Scourfield et al., 2003; Van Der Valk, Van Den Oord, Verhulst, & Boomsma, 2003; Zavos, Rijsdijk, & Eley, 2012), contributing to their continuation over time. Research of this kind is of great importance when it comes to understanding the genetic effect on the developmental trajectory of depression and anxiety. However, despite considerable evidence for the role of genetic and environmental effects in the aetiology and development of depression and anxiety, twin studies do not provide any information on the specific environments or genetic variants that are involved.

1.1.1. Environmental effect on depression and anxiety

For decades studies examining environmental effects on depression and anxiety have consistently demonstrated the importance of stressful or negative life events as factors significantly associated with both disorders (Bidzińska, 1984; Billings, Cronkite, & Moos, 1983; Blazer, Hughes, & George, 1987; Boer et al., 2002; Brown, Bifulco, & Harris, 1987; Brown, Harris, & Peto, 1973; Eley & Stevenson, 2000; Constance Hammen, Marks, Mayol, & DeMayo, 1985; Holahan & Moos, 1991; Lloyd, 1980; Patrick, Dunner, & Fieve, 1978; E. Paykel, 1979; E. S. Paykel et al., 1969; Rapee & Szollos, 2002; Shrout et al., 1989; Thomson & Hendrie, 1972; Williamson, Birmaher, Anderson, Al-Shabbout, & Ryan, 1995). Many of these studies have demonstrated a greater number of stressful or negative life events reported by those with depression (Brown et al., 1973; E. S. Paykel et al., 1969; Thomson & Hendrie, 1972) and anxiety (Boer et al., 2002; Eley & Stevenson, 2000; Rapee & Szollos, 2002), leading

to the belief that such events represent significant factors in the development and maintenance of both depression (A. T. Beck, 1976; K. S. Kendler, Karkowski, & Prescott, 1999) and anxiety (Chorpita & Barlow, 1998; Hudson & Rapee, 2004; Rapee, 2001). Consistent evidence from such research suggests that the occurrence of stressful or negative life events are significantly associated with both depression and anxiety. However, due to variations in how such life events are measured, the magnitude of these associations tends to be different across studies. Despite this, there is also consistent evidence for a dose-response relationship between such life events and depression and anxiety, with the occurrence of more severe events having the strongest associations. These studies also demonstrated stressful or negative life events as highly prevalent, although whilst the majority of those with depression and anxiety do report these events prior to onset, only a small amount of those having experienced such events go on to develop depression or anxiety.

These effects have also been shown in depressed and anxious children (Goodyer & Cooper, 1993; Loss, Beck, & Wallace, 1995; Tisher, Tonge, & de Horne, 1994). For example, in a study by Tisher et al. (1994), 20 children with depression were assessed in comparison to 88 clinically non-depressed children and 55 normal children with ages ranging from 7-11. The study used the Children's Depression Inventory (Maria Kovacs, 1981), to assess depression and the Recent Life Events and Stressor Scale (Tisher, 1992) to assess stressful life events over the last 12 months. Findings demonstrated that the group of depressed children scored significantly higher on both the Recent Life Event and Stressor scale compared to those in the non-depressed and normal groups. In a later study, Boer and colleagues (2002) demonstrated significant differences between the number of negative life events reported by children aged 8-13 with clinical anxiety in comparison with numbers reported by healthy controls and their nearest non-anxious sibling aged 6-13. Due to the age of the children, parent reports of life events were obtained using The Questionnaire of Life Events (QLE) which was adapted from Coddington's Social Readjustment Rating Questionnaire (Coddington, 1972a, 1972b). Findings revealed that those with anxiety disorder experienced significantly more negative life events than their matched controls and nearest siblings, including across both their shared and non-shared environments.

However, whilst there is a wealth of evidence suggesting that greater numbers of stressful or negative life events are associated with episodes of depression and anxiety, there is a key methodological issue which presents a problem when attempting to make causal inferences regarding the effects of such events. Although often an unavoidable method of data

collection in such research, the use of self-report questionnaires to assess the occurrence of past life events are vulnerable to retrospective recall bias, and mood congruency effects, as recall accuracy may be impaired, especially in those with current disorders. For instance, a vast majority of early studies, often using such an approach, failed to consider whether the presence of depression or anxiety affected the reporting accuracy of life events, or indeed whether they occurred before or after symptoms of said disorders. For example, with particular regards to depression, it has been noted that depression itself can be a causal factor in experiencing particular events (Constance Hammen, 1991), and that those with a history of depression, whether experiencing an episode or not, tend to experience more events than those with no such history (Kessler & Magee, 1993). In keeping with this concern, research has noted a stronger association between "dependent" life events (those more likely a result of the participants own action) and depression versus that of "independent" life events (those more likely the result of much more uncontrollable external factors) and depression (Williamson et al., 1995), suggesting a possible bias in the reporting of such events due to the presence of depression. Research that has examined both dependant and independent events and found evidence for independent life events as predictors of depression and anxiety has made a case for such life events as potential causal factors of these disorders. For example, a later study by Williamson et al. (2005) demonstrated that whilst depressed children did experience more dependant life events than their anxious or control counterparts, they also experienced significantly more independent life events than both groups. Furthermore, these effects were specific to depression and not anxiety. In contrary to Williamson et al.'s (2005) findings regarding anxiety, more recent research examining the differences in self-reported life events in anxious children has highlighted independent life events as associated with the onset of anxiety (J. L. Allen, Rapee, & Sandberg, 2008; Goodyer, Wright, & Altham, 1990), as well as a significantly greater number of dependant life events compared to controls (J. L. Allen & Rapee, 2009). This could suggest a fundamental difference in the effect of dependant and independent life events such that independent life events are more likely to trigger the onset of depression and anxiety, whilst dependant life events are more likely associated with the maintenance and recurrence of the disorders depending on the event type (threat or loss). However, as noted above, only a minority of those who have experienced such life events go on to develop either disorder.

1.1.2. Genetic effect on depression and anxiety

Early efforts by candidate gene studies to identify genetic variants associated with depression and anxiety highlighted many single nucleotide polymorphisms (SNPs). The candidate gene approach itself selects variants *a priori* due to their assumed involvement in the biology of the disorders. Such studies have had some success, demonstrating associations between depression and anxiety and variants in catechol-O-methyltransferase (COMT) (Craddock, Owen, & O'Donovan, 2006; N. R. Wray et al., 2008), Brain derived neurotrophic factor (BDNF) (Frustaci, Pozzi, Gianfagna, Manzoli, & Boccia, 2008; Verhagen et al., 2010), and 5-Hydroxytryptamine (serotonin) receptor 2A (HTR2A) (Christiansen et al., 2007) amongst others. However, many of these findings failed to replicate in further studies, potentially due, in part to insufficient sample sizes and a focus on only a small number of candidate genetic variants. This suggests that the search for genetic associations with depression and anxiety should move beyond the assessment of just a handful of candidate genetic variants, and instead assess whole genome data in more sufficiently powered samples. This suggestion is further supported by a recent study that utilized large-scale population and case-control samples (subsamples ranging from 62,138 to 443,264) to examine 18 candidate variants previously implicated in 10 or more candidate gene studies of depression (Border et al., 2019). Here, the authors reported no clear evidence that any of the candidate variants had a main effect on depression phenotypes in samples much larger than those of previous candidate gene studies which had frequently reported large effects.

More recent genome-wide association studies (GWAS) have made it possible to assess the whole genome for associations with psychiatric disorders by assaying upwards of 500,000 variants simultaneously. This increased coverage means that, in contrast to candidate gene studies that tend to focus on individual variants, GWAS are able to take a hypothesis-free approach which does not require any a priori assumptions regarding the role of specific genes in a disorder. This hypothesis-free approach brings with it a substantial multiple-testing burden resulting in a stringent genome-wide significance threshold of $p<5\times10^{-8}$ in order to protect against false positives. Initial GWAS were limited by inadequate sample sizes to detect variants of small effect at genome-wide significance. However, the formation of consortia and the pooling of data have made mega-analysis and meta-analysis possible, resulting in substantial progress in identifying replicable variants associated with specific disorders. To date, GWAS have discovered 102 genome-wide significant variants for depression in a sample of 807,553 (Howard et al., 2019), and five for anxiety disorders in a sample of 114,000 (Purves et al.,

2017). However, the path of discovery for both depression and anxiety has been marred by several issues some of which are shared between them. For example, small sample sizes and aetiological heterogeneity represent problems in terms of GWAS for both depression and anxiety, whilst for anxiety complex comorbidity, and issues distinguishing between normative and pathological anxiety (McGrath, Weill, Robinson, MacRae, & Smoller, 2012) present further problems. For depression a further issue includes the modest heritability of 37%, resulting in smaller effects sizes of risk alleles (Sullivan, Kendler, & Neale, 2003; Sullivan et al., 2000). Sample sizes 4-5 times greater than the largest GWAS for schizophrenia, which has a heritability estimate of 80% (Cardno & Gottesman, 2000; Sullivan et al., 2003) are needed to deal with the lower heritability and capture the same amount of genetic variance (N. Wray et al., 2012).

New polygenic approaches such as the use of polygenic risk scores (PRS), are making some progress in closing the gap between heritability estimate from quantitative genetic studies and those from molecular genetic studies. This approach simultaneously takes into account the effect of all genotyped variants, including those that do not reach genome-wide significance, to make a single PRS, the effect of which, on a given phenotype, is determined through linear or logistic regression which also includes a proportion of variance explained (N. R. Wray et al., 2014). Studies using such polygenic approaches have demonstrated that the aggregate effect of common variants explain considerably more of the proportion of heritability found in twin studies in comparison with GWAS (Okbay et al., 2016; N. R. Wray et al., 2018). They have also confirmed findings from previous bivariate twin studies highlighting considerable genetic overlap between phenotypes such as depression, anxiety and subjective wellbeing showing correlations ranging from r=.33 to r=.88 (Okbay et al., 2016).

Previous research has demonstrated that a PRS can predict a small yet significant proportion of the variance in psychiatric disorders such as depression and anxiety. For example, one study tested a depression PRS, defined from a discovery GWAS of 1,738 adult cases and 1,802 controls aged between 18-65, in two separate target samples of adults and elderly individuals aged approximately 45 years and over (Demirkan et al., 2011). Both target samples were assessed for depression and anxiety, and collectively contained 400 depression and anxiety cases and 1,205 controls. Results showed the depression PRS as explaining up to 1% of variance in depression across the two target samples. Interestingly, up to 2.1% of the variance in anxiety were explained by the depression PRS suggesting a shared genetic architecture between the two psychopathologies. The authors also noted the stability of the

PRS over time, as whilst the highest amount of variance explained was within the elderly sample, the increase was minimal, suggesting that these genetic influences on depression and anxiety change very little over time, however this was not assessed longitudinally. Whilst this study demonstrates that a depression PRS can explain some variance in both depression and anxiety it, like other studies that followed only examined these psychopathologies within adult and elderly samples (Levine et al., 2014). However, there are also a handful of studies that have assessed main effects of a PRS, both longitudinally and cross-sectionally within samples of children and/or adolescents. These have, for example, involved a PRS for schizophrenia and educational attainment in association with early childhood behavioural problems (Jansen et al., 2018), and an attention deficit/hyperactivity disorder PRS predicting problems with attention in children (Groen-Blokhuis et al., 2014).

This relatively novel approach of using a PRS for one specific phenotype to predict variance in others has also highlighted several cross-phenotype associations in other recent studies. For example, a recent systematic review, that included 25 studies, has shown how both an major depressive disorder (MDD) and bipolar disorder (BD) PRS can predict a range of psychiatric disorders including depression, bipolar, schizophrenia, as well as other phenotypic outcomes such as creative professions and higher educational attainment (Mistry, Harrison, Smith, Escott-Price, & Zammit, 2018). This review demonstrated that across most of the phenotypes assessed, both PRSs explained a small, but significant amount of the variance (<2%). These types of cross-phenotype associations have also been shown in two longitudinal studies of children (H. J. Jones et al., 2016; M. G. Nivard et al., 2017), each of which using the same PRS for schizophrenia (Purcell et al., 2009). Evidence for heterotypic continuity was highlighted, as the schizophrenia PRS, which was created from GWAS summary statistics of European adults, was associated with childhood psychopathology, including depression and anxiety across both studies. These findings provide strong evidence for the development of childhood psychopathology as a potential precursor to more severe psychiatric disorders in adulthood. Furthermore, if these psychopathologies do robustly precede later, more severe psychiatric disorders, they may represent important mediators through which later problems occur. These studies, whilst important in their own right, also serve as proof of principle for this polygenic approach. However, the small fraction of variance explained by such genome-wide approaches remains problematic.

1.1.3. Gene-by-environment interaction effects on depression and anxiety

The research discussed above provides substantial evidence for the importance of both genetic and environmental effects on depression and anxiety. However, as complex disorders these genetic and environmental effects are not thought to act in isolation, and it is likely the complex interplay between both, that lead to the development and maintenance of such disorders (Gratten, Wray, Keller, & Visscher, 2014).

Candidate gene-by-environment (GxE) interaction studies have assessed a number of genetic variants previously implicated in candidate gene studies of depression and anxiety, examining how variations in the expression of a selected candidate genetic variant moderate the effects of environments such as childhood maltreatment and stressful life events. One example is the much assessed 5-HTTLPR (a putatively functional genetic variant in the gene encoding the serotonin transporter). In a seminal GxE study by Caspi and colleagues (Caspi et al., 2003) it was suggested that major depression was influenced by an interaction between the 5-HTTLPR and stressful environments. Caspi and colleagues demonstrated that despite the lack of a main genetic effect, those with the short (S)-allele of the serotonin transporter polymorphism were at higher risk for depression following stressful life events or childhood maltreatment. This association, has been given further support by a large scale meta-analysis (Karg, Burmeister, Shedden, & Sen, 2011), which was consistent with the findings of two qualitative reviews (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Uher & McGuffin, 2010), all of which considered the same 54 publications. Similar findings have subsequently been reported for anxiety disorders. For example, Stein and colleagues (Stein, Schork, & Gelernter, 2008) reported that S-allele homozygotes, having experienced childhood maltreatment, had higher anxiety sensitivity, a potential intermediate phenotype of both anxiety and depression, in comparison to heterozygotes or homozygote L carriers. In another study it was demonstrated that those with one or both S-alleles exhibited elevated anxious mood when presented with higher levels of daily stress measured using daily monitoring techniques (Gunthert et al., 2007). However, it is important to note that these effects have been highly debated and that there have also been negative meta-analyses regard the moderation of stressful life events by 5-HTTLPR on depression (Risch et al., 2009).

Other candidate GxE studies in both depression and anxiety have also found evidence for significant interactions between environmental factors such as childhood maltreatment and stressful life events, and candidate genes including brain derived neurotrophic factor (BDNF) (Bukh et al., 2009; J Chen, Li, & McGue, 2012; Hosang, Shiles, Tansey, McGuffin, & Uher,

2014), Dopamine receptor D2 (DRD2) (Elovainio et al., 2007), Corticotropin-releasing hormone receptor 1 (CRHR1) (Liu et al., 2013; Polanczyk et al., 2009), catechol-O-methyltransferase (COMT) (Mandelli et al., 2007), and FK506 binding protein 5 (FKBP5) (Zimmermann et al., 2011). However, with regards to depression, Border et al (2019), who found no evidence for significant main effects of 18 candidate variants previously implicated in multiple depression candidate gene studies on depression phenotypes, also demonstrated similar findings regarding candidate GxE interactions. That is, they found no evidence of any significant moderating effects regarding the 18 candidate variants and environmental factors including, sexual or physical abuse during childhood and socioeconomic adversity, on depression phenotypes.

Traditionally, the majority of these candidate GxE studies adopted the conceptual framework of the *Diathesis-Stress* model (Monroe & Simons, 1991). According to this model, the detrimental effects of adverse environmental influences only lead to psychopathology when combined with an inherent vulnerability of the individual. Specifically, The Diathesis-Stress model suggests that some individuals are more vulnerable to adverse environmental influences (e.g., negative life events), as a function of their specific biological (e.g., genetic) and/or psychological (temperament) make-up, but that in the absence of such adversity, these inherent vulnerabilities are not sufficient to lead to psychopathology. Furthermore, individuals who do not succumb to the negative effects of environmental stressors, either as the function of not carrying these genetic vulnerabilities or due to the presence of other protective factors, are deemed resilient.

However, as highlighted above, such candidate GxE studies, despite their important contribution to the understanding of psychiatric disorders have several limitations. Firstly, whilst a strong biological hypothesis is required for the selection of appropriate candidate genetic variants, the biological mechanisms underlying these disorders are still somewhat limited, sometimes resulting in the selection of inappropriate candidates. Secondly, findings from candidate gene studies have been notoriously difficult to replicate with few candidates showing the same effect across separate samples and with several meta and mega-analyses contradicting initial results. Thirdly, recent research in psychiatric genetics has provided robust evidence suggesting that the genetic effect for most disorders, including depression and anxiety, is made up of thousands of genetic variants of small effect rather than individual variants of large effect. Lastly, the Diathesis-Stress conceptualization of GxE has recently been challenged by the *Differential Susceptibility Theory* (DST: (Jay Belsky, Bakermans-

Kranenburg, & Van IJzendoorn, 2007; Jay Belsky & Pluess, 2009a), which suggests that individuals differ in their general susceptibility to both negative *and* positive environmental influences. According to DST, those individuals who are genetically more susceptible to environmental influences are more likely to develop psychopathology in response to the adverse effects of stressors. However, higher genetic susceptibility may also make these individuals disproportionately likely to benefit from positive and supportive environmental influences. Hence, higher susceptibility may function in a "for better and for worse" manner (Jay Belsky, Pasco Fearon, & Bell, 2007). Consequently, resilience as observed in the Diathesis-Stress model may reflect "low susceptibility" to environmental influences with vulnerability reflecting "high susceptibility". Building on this theory, Pluess and Belsky (2013) have conceptualized individual differences in response to positive environmental influences more specifically in the *Vantage Sensitivity* framework. According to Vantage Sensitivity, some people are more likely to benefit from the positive effects of supportive experiences than others as a function of inherent characteristics, including genetic differences (Pluess, 2017).

More recently efforts have been made to use genome-wide data to examine GxE interactions adopting the theoretical framework of Differential Susceptibility and examine multiple variants across the genome that may moderate the effects of the environment on psychiatric disorders. For example, genome-wide environmental interaction studies (GWEIS), which assess interactions between specific environments and each SNP across the genome independently have investigated associations with environmental factors such as stressful life events, thus far on depression only (Dunn et al., 2016; Ikeda et al., 2016; Otowa et al., 2016). However, although in their infancy, the majority of significant findings thus far have either failed to replicate (Dunn et al., 2016) or not survived correction for multiple testing (Otowa et al., 2016). This likely suggests that GWEIS is still somewhat underpowered to detect these effects, and further highlights the statistical complexities regarding the combination of GWAS and environmental moderators.

Polygenic approaches such as PRS-by-environment interaction studies have also been conducted demonstrating significant interactions between the same MDD PRS and childhood trauma (Mullins et al., 2016; Peyrot et al., 2014) but with conflicting results. Whilst the reason for such discrepancy between these studies is unclear, methodological differences regarding the measurements of childhood trauma could have been a factor in terms of such conflicting findings. Other studies have included cross-sectional PRS-by-stressful life events on depression symptoms (Musliner et al., 2015) and MDD (Mullins et al., 2016), both of which

demonstrated no significant interaction, and a highly successful longitudinal study, demonstrating an MDD PRS as consistently moderating levels of depression following a specific event (i.e. death of a spouse) (Domingue, Liu, Okbay, & Belsky, 2017).

Despite some early environmental measurement issues, PRS GxE research whilst still in its infancy is providing some promising findings. However, it is important to note that this approach relies on the untested assumption that genes implicated in case-control studies of psychiatric disorders, and therefore genes with a main effect on the disorder of interest, are the same genes implicated in GxE which moderate the effect of the environment on the same disorder. Furthermore, whilst these findings are relevant, they tend to explain only a small percentage of the variance in depression and anxiety. Therefore, it becomes important to shift focus to potential intermediate phenotypes, such as cognitive biases, that may exist on a pathway to these disorders.

1.2. The effect of cognitive biases on affective states and disorders

1.2.1. Cognitive theories of depression and anxiety

To date, Beck's cognitive theory of depression (A. T. Beck, 1967, 1983) remains one of the most recognised and supported theories amongst the literature regarding the effects of cognitive biases on affective states and disorders. His theory suggests that the aetiology of the depression is influenced by biased cognition impacting on how information is acquired and processed. More specifically, Beck suggested that depressed individuals possess schemas (internal mental representations) that affect their perception of themselves and their environment. These schemas which embody elements of loss, failure, worthlessness and rejection cause those with depression to have a cognitive triad of negative views regarding themselves, the world around them, and the future. An important feature posited by Beck's theory is that childhood and adolescent adversity is responsible for the development of these negative schemas, which in turn increase susceptibility to depression. These schemas, once in place, can then be triggered by negative life events from either internal or external sources. It is these characteristics that are said to contribute to the negative mood states observed in those with depression. Furthermore, and of great importance, Beck suggested that even following recovery from an episode of depression the presence of these negative schemas would remain. These latent negative schemas, if triggered by a negative event, could then result in the rise of negative thoughts and moods going some way to explaining both first onset as well as future episodes of depression.

Beck's original theory resulted in much subsequent research by himself and others (A. Beck, Emery, & Greenberg, 1985; Bower, 1981, 1987) who continued to build on and develop this theoretical perspective. However, a later more nuanced theoretical model coming from a perspective of cognitive psychology proposed that depressive and anxious mood states may be associated with differential patterns of cognitive processes (J. M. Williams, Watts, MacLeod, & Mathews, 1988). Briefly, the model suggested that the distribution of cognitive resources may be impacted by anxious and depressive mood states at different levels of information processing. However, following an extensive review of new literature nearly a decade later it was concluded that whilst there was evidence for such dissociation regarding the nature of cognitive biases in anxiety and depression findings were not consistent (J. Williams, Watts, Macleod, & Mathews, 1997). Since then, findings have remained mixed, with many not in keeping with such a distinction (for comprehensive review see (Mathews & MacLeod, 2005b)).

Despite this, the core premise remained that for depression, and also anxiety, negatively biased cognitive processing of information can trigger the onset, maintenance and recurrence of these psychopathologies. In support of these theories selective cognitive processing regarding attention, interpretation and memory have been shown to be highly important factors in the development, maintenance and recurrence of both depression and anxiety (A. T. Beck & Clark, 1997; Ingram, 1984; LeMoult & Gotlib, 2019; Muris & Field, 2008; Teasdale, 1988).

1.2.2. Cognitive biases

Cognitive biases represent a departure from normal or rational judgement, whereby illogical inferences are made regarding other individuals or situations (Haselton, Nettle, & Murray, 2005). There is also strong evidence to suggest that emotional vulnerability, a risk factor for both depression and anxiety, is associated with cognitive biases that magnify threat-related information and negativity, relative to benign or positive information (Cisler & Koster, 2010; Dudeney, Sharpe, & Hunt, 2015; Fox, 2008; I. H. Gotlib & Joormann, 2010; Lau & Waters, 2017; Mathews & MacLeod, 2005b). Selective cognitive biases such as attention, interpretation and memory biases are often associated with mood-related outcomes (Cisler & Koster, 2010; Dudeney et al., 2015; I. H. Gotlib & Joormann, 2010; Lau & Waters, 2017). Furthermore, there is a growing body of literature suggesting that depressed individuals fail to exhibit positive cognitive biases when compared to their healthy control counterparts (Alloy & Abramson, 1979; Canli et al., 2004; I. H. Gotlib, Jonides, Buschkuehl, & Joormann, 2011). Such cognitive biases have therefore been suggested as potential mechanisms for the

development and maintenance of both depression and anxiety. In particular, attentional bias towards threat has been consistently associated with anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Mathews & MacLeod, 2005b), and to some extent depression (Ian Gotlib, Krasnoperova, Yue, & Joormann, 2004), whilst interpretation biases have been said to play a possible causal role in the onset and maintenance of depression (Joormann & Gotlib, 2010). Memory bias, in the form of a bias recall for negative information has also been consistently reported in studies of depressed individuals (I. H. Gotlib & Joormann, 2010).

1.2.3. Attention bias

The first of these, Attention bias, refers to the automatic preferential processing of specific categories of information (e.g., positive versus negative valence) in the environment. Research has also suggested that attention bias for positive stimuli may represent an enhancing bias related to resilience (Raila, Scholl, & Gruber, 2015). Such bias in attentional processing is often measured using the dot-probe task which assesses reaction time to a probe in association with emotional valanced stimuli. While attention biases towards threat-related information has been associated with anxiety in both adults (Cisler & Koster, 2010) and children (Dudeney et al., 2015), biases towards negative stimuli is also characteristic of depression (Peckham, McHugh, & Otto, 2010). However, whilst depressed individuals have shown expected patterns of negative attention bias when observing sad versus happy or angry stimuli (Ian Gotlib et al., 2004), results have tended to differ as a consequence of the duration that the stimuli are displayed. For example, when stimuli are displayed for short durations negative attention bias in depression is not observed (Mogg, Bradley, & Williams, 1995). However, when stimuli are displayed for longer periods a negative attention bias is observed (Donaldson & Lam, 2004; Ian Gotlib et al., 2004; Joormann & Gotlib, 2007; Peckham et al., 2010), and in one particular case predicted depression onset in at risk adolescents (Jenness, Young, & Hankin, 2017). The use of faces rather than words also provides more consistent evidence for attention bias in depression (Armstrong & Olatunji, 2012). This, and earlier research examining associations between anxiety and attention bias (Fox, Russo, Bowles, & Dutton, 2001; Fox, Russo, & Dutton, 2002; Georgiou et al., 2005), and later applied to depression (Koster, De Raedt, Goeleven, Franck, & Crombez, 2005), has led to the hypothesis that anxiety and depression are characterized not simply by biases towards negative stimuli, but also difficulty in disengaging from negative stimuli that has been attended to (for comprehensive review see

(Mathews & MacLeod, 2005b)). In keeping with this hypothesis depressed children and adolescents (R. H. Jacobs, Reinecke, Gollan, & Kane, 2008), as well as those at familial risk, have been shown to have negative attention biases following negative mood induction (Joormann, Talbot, & Gotlib, 2007; Kujawa et al., 2011), with negative attention bias also being shown to predict depressive symptom onset (Beevers & Carver, 2003).

The causal role of attentional biases in anxiety and depression has also been suggested by studies using cognitive bias modification (CBM) techniques to modify attention bias. These studies, which aim to train an individual's attention away from threatening or negative stimuli have been shown to result in reduced anxiety in clinical and non-clinical samples (Hakamata et al., 2010; Hallion & Ruscio, 2011). Furthermore, research using a dot-probe version of CBM has demonstrated reduced negative attention and increased attention to neutral stimuli in depressed university students (Wells & Beevers, 2010; Yang, Ding, Dai, Peng, & Zhang, 2015), and adolescents (Yang, Zhang, Ding, & Xiao, 2016) across multiple training sessions. One study also demonstrated that attention bias training based on the dot-probe task modified attention bias as well as emotional and physiological stress responses in young individuals at high familial risk for depression over six sessions (LeMoult, Joormann, Kircanski, & Gotlib, 2016). However, results have not been consistent with several studies finding no significant effects of CBM across single (Kruijt, Putman, & Van der Does, 2013), or multiple (Baert, De Raedt, Schacht, & Koster, 2010) training sessions. It is possible that the choice of training task can influence both the effectiveness of the training and transference to other domains of function, with the dot-probe based training paradigm being the most successful to date.

1.2.4. Interpretation bias

Interpretation bias, which refers to the tendency to interpret ambiguous situations as either positive or negative, has also been associated with both anxiety and depression (A. T. Beck & Clark, 1997), with research suggesting that it may play a causal role in the onset and maintenance of depression (Lawson, MacLeod, & Hammond, 2002; Mathews & MacLeod, 2005b). More recently, there has been increasing amount of evidence suggesting that individuals with depression make more negative interpretations regarding ambiguous information (Lee, Mathews, Shergill, & Yiend, 2016; Orchard, Pass, & Reynolds, 2016). Depressed individuals, when compared to their non-depressed counterparts, have consistently demonstrated more negative interpretation bias across a range of tasks. These include homophone tasks (Mogg, Bradbury, & Bradley, 2006), where words with positive/negative or

neutral meanings (e.g. gilt, guilt) are listen to, and interpreted; ambiguous scenarios tasks (Butler & Mathews, 1983), where hypothetical ambiguous scenarios are interpreted as either positive or negative, as well as other (Lawson et al., 2002; Voncken, Bögels, & Peeters, 2007). Furthermore, research has demonstrated negative interpretation bias in adolescent and adult alike (Orchard et al., 2016), across social and non-social situations (Voncken et al., 2007), and has been shown to be greater, when interpreting emotionally ambiguous information, as depression severity increases (Lee et al., 2016). Evidence of interpretation bias in those without depression has also been documented, with one study finding negative interpretation bias in a sample of girls at risk of depression but yet to experience an episode (Dearing & Gotlib, 2009), giving more gravity to its possible casual role.

Similar to attention bias, modification of biases in the interpretation of ambiguous situations has also been shown to reduce clinical symptoms of affective disorders (Hallion & Ruscio, 2011). Studies using interpretation bias modification (CBM-i) to change interpretation biases have been a useful tool for testing the hypothesized association between interpretation biases and depression and have demonstrated that the modification of interpretation bias in depressed individuals is possible (Joormann, Waugh, & Gotlib, 2015; LeMoult et al., 2018). However, findings are not robust as there have been several studies that have provided exceptions to the research described above, whereby no association was found between psychopathology and interpretation bias (Bisson & Sears, 2007; Lawson & MacLeod, 1999), possibly indicating the instability or dynamic nature of this bias and/or issues regarding its measurement.

1.2.5. Memory bias

Memory bias, referring to the tendency to selectively remember positive or negative information has, particularly in the case of a memory bias for negative self-referential information, been shown to be characteristic of depression (I. H. Gotlib & Joormann, 2010). This effect is found most consistently when explicit, rather than implicit memory is assessed. Furthermore, within depression, explicit memory biases seem to be specifically associated to stimuli relevant to depression rather than negative stimuli in general (IH Gotlib, Roberts, & Gilboa, 1996). However, whilst depressed individuals tend towards negative versus neutral stimuli, they also fail to exhibit a preferred tendency to recall positive versus neutral stimuli present in healthy individuals with no history of psychiatric disorder (IH Gotlib et al., 1996; Matt, Vázquez, & Campbell, 1992). Interestingly, evidence has suggested that memory biases

regarding positive stimuli maybe associated with how information is initially encoded. Whilst healthy participants tend towards encoding positive information, individuals with depression do not display this bias (I. H. Gotlib et al., 2011). This could highlight a need to distinguish between a bias in memory and a bias in encoding as separate processes. Other ways in which depressed individuals differ from healthy controls is through their recall of autobiographic memory, a trend that has been observed across different cultures (Dritschel, Kao, Astell, Neufeind, & Lai, 2011). Furthermore, overgeneral autobiographical memory (J. M. Williams & Broadbent, 1986), which refer to an individual's tendency to retrieve general rather than specific memories in response to a cue word, has been demonstrated in depressed individuals (J. M. Williams et al., 2007), and said to increase depression risk in adolescents (Rawal & Rice, 2012). These finding are in line with previous studies suggesting that overgeneral autobiographical memories in depressed individuals limit their ability to correct a negative mood using these same memories (C. Chen, Takahashi, & Yang, 2015; Joormann, Siemer, & Gotlib, 2007). A recent study has also demonstrated that a positive memory bias can have a significant protective effect against symptoms of depression one year on by reducing the negative effect of stressors across time (Askelund, Schweizer, Goodyer, & van Harmelen, 2019b). Furthermore, much like attention and interpretation bias, CBM studies of memory bias, despite being in their early stages, have provided evidence to suggest that training individuals memory biases can decrease both depressive symptoms and rumination (E. R. Watkins, Baeyens, & Read, 2009).

These studies, and particularly those regarding the successful implementation of CBM, provide some support for cognitive biases as a potential mechanism through which depression and anxiety occur and continue to persist. However, as highlighted above, and further demonstrated by recent systematic reviews and meta-analyses, findings from CBM studies, with particular regards to their effect on affective disorders, have to date been somewhat inconsistent. For example, a review of meta-analyses regarding attention and interpretation CBM studies demonstrated that whilst both ABM and CBM-i were successful at modifying attention and interpretation bias respectively (Jones & Sharpe, 2017), the effects were more evident in adults compared to children, possibly due to a lack of studies that included children. Furthermore, whilst both ABM and CBM-i were shown to improve anxiety symptoms in adults across all meta-analyses that included the measure, their effect on depressive symptoms were far less evident with only two out of seven meta-analyses highlighting a reduction in depression symptomology. However, these findings stand in contrast to a previous review and meta-

analysis that noted whilst ABM and CBM-i improved attention and interpretation bias, there were no conclusive benefits for depression and anxiety outcomes (Pennant et al., 2015).

In a more recent meta-analysis of randomised controlled trials comparing ABM and CBM-i with control conditions and other CBM approaches, small yet consistent benefits of CBM-i for anxiety, and to a similar extent comorbid depression were noted, with ABM demonstrated as largely ineffective (Fodor et al., 2020). However, the authors also questioned the reliability of their findings, suggesting that these effects could fluctuate across a wide range in future trials due to the large confidence intervals observed as well as the varying reliability of CBM tasks, potentially adding to further inconsistencies regarding the effects of CBM on specific affective disorders.

Despite the inconsistencies regarding CBM, it is thought that integrating this line of research with that of the broad range of genetic and environmental theory, that have classically remained separate, could provide a unique and novel insight into the development of these highly prevalent and debilitating disorders.

1.3. Integrating cognitive, genetic, and environmental theory

1.3.1. Aetiology of cognitive biases

While there is substantial literature linking cognitive biases with psychopathology, far fewer studies have explored how and why these cognitive biases emerge. Theoretical perspectives, such as Beck's original theory (A. Beck, 1967), make little mention about cognitive biases being heritable, suggesting, as mentioned above, that they develop as a result of early childhood adverse experiences. However, in an update to Beck's original theory, a more unified model of depression has been proposed integrating clinical, cognitive, biological, as well as evolutionary perspectives (Beck & Bredemeier, 2016). Here, the authors considered both biological factors, including genetic variation and physiological stress reactivity as well as environmental factors such as early adversity and trauma in the development of negative information processing biases and in turn depression.

In support of this more recently updated theory, findings from twin studies have also demonstrated that a number of cognitive biases are, at least partly heritable. For example, a twin study assessing interpretation bias in children measured using both a homophone task and ambiguous scenarios task found heritability estimates of 30% for the homophone ambiguous

words task, with shared environmental effects accounting for 2%, and the remaining 68% accounted for by non-shared environmental factors (Eley et al., 2008). As testament to the validity of the measures, the estimates for the ambiguous scenarios task were very similar to that of the homophone task, with a heritability estimate of 24%, shared environment estimated at 7%, and non-shared environmental effects accounting for the remaining 69%.

Similar heritability estimates have also been reported for memory bias. Rijsdijk et al (Rijsdijk et al., 2009) measured memory bias by assessing the recall of both pleasant and unpleasant words, in a sample of 125 female twin pairs aged between 18 and 30. The authors reported that the heritability of the proportion of unpleasant words recalled was 30% with the remaining variance explained by the non-shared environment (64%) and the shared environment (6%). The recall of pleasant words showed a similar estimate for the non-shared environment (63%), slightly lower heritability (23%) and a higher contribution of the shared environment (14%).

The same study also assessed attention bias using a dot-probe task to measure the reaction time to both neutral and threat valanced faces with estimates regarding reaction time given for both the left and right fields of vision. Findings demonstrated that neutral stimuli in the right field of vision had a heritability estimates of just 3% (43% shared environment; 54% non-shared environment) for neutral stimuli, and 2% (41% shared environment; 57% non-shared environment) for threatening stimuli. Interestingly, in the left field of vision, heritability estimates were dramatically higher with an estimate of 49% (16% shared environment and 35% non-shared environment) for neutral stimuli, and 42% (18% shared environment; 41% non-shared environment), for threatening stimuli. This would seem to suggest that not only are the reaction times in the left field of vision more genetically determined than in the right, but also that attention bias in the left field of vision is under far more genetic influence. The reasons for this are somewhat unclear, however, these may be chance findings caused by the poor reliability of the dot probe task. For instance, although rarely conducted, split half reliability of the dot-probe task has been shown to be very low, ranging from -0.12-0.68 (Parsons, Kruijt, & Fox, 2018; Price et al., 2015b; Staugaard, 2009). Studies using more reliable attention bias measures such as those involving event related potentials show far more robust heritability estimates ranging between 0.40-0.55 in both adolescents (Anokhin, Golosheykin, Grant, & Heath, 2010) and adults (Weinberg, Venables, Proudfit, & Patrick, 2014).

In addition to biases in attention, interpretation and memory, anxiety sensitivity has also been assessed in both children and adults (Silverman, Ginsburg, & Goedhart, 1999; Stein,

Jang, & Livesley, 1999). Anxiety sensitivity is a measure of one's sensitivity to physical and emotional anxiety symptoms (attentional bias), as well as a perception of them as harmful (interpretational bias (Reiss, Peterson, Gursky, & McNally, 1986)) and can be reliability measured in children using The Child Anxiety Sensitivity Index (CASI: (Silverman, Fleisig, Rabian, & Peterson, 1991)), a questionnaire with good internal consistency (.93) and test re-test reliability (Silverman et al., 1991). One study using the CASI in a sample of 300 twin pairs aged 8 years old reported a heritability estimate of 37% for anxiety sensitivity, with non-shared environmental estimates responsible for the remaining 63% (Eley, Gregory, Clark, & Ehlers, 2007). However, in an earlier study assessing anxiety sensitivity in adults, the heritability estimate was found to be 50% with non-shared environments accounting for the remaining variance (Stein et al., 1999). This increase in heritability may be due to slight measurement variations between the CASI which uses a 3-point Likert scale, and the Anxiety Sensitivity Index used for adults which uses a 5-point Likert scale. It is possible that allowing for greater variations in the adult measures of anxiety sensitivity may have increased heritability estimates. However, evidence from other studies suggests that genetic effects on traits, including cognitive biases, do increase from childhood into adulthood as new genetic influences become active. For example, a twin study examining attributional style (the explanation to one's self regarding why an event was experienced as either positive or negative), found heritability estimates of 35% in a large sample of 15-year-olds (Lau, Rijsdijk, & Eley, 2006). At a two year follow up involving the same sample the heritability estimate for attributional style had increased to 44% (Lau & Eley, 2008).

These studies lend support to Beck & Bredemeier's (2016) more recent unified model, demonstrating the significant role of both genes and the environment in the development of cognitive biases. However, while these studies suggest that the environment does play a strong role, with non-shared environments appearing to be more important than shared environments or genetic influences, it is important to note that the non-shared environmental component of the twin model also includes measurement error. This is an important factor to consider as it means that this component could include percentage of non-shared environmental influences, error of measurement, or both. Furthermore, as mentioned earlier, information regarding which environments are causing such effects cannot be determined using a twin studies design.

1.3.2. Environmental influences on cognitive biases

Studies examining specific environmental factors have demonstrated the importance of their effect on the development of cognition. Early adversity including childhood maltreatment and negative parenting practices such as increased criticism, an absence of warmth, and verbal humiliation have all been suggested to lead to the development of negative cognitions (Fani, Bradley-Davino, Ressler, & McClure-Tone, 2011; Rose & Abramson, 1992).

Thus far, the majority of studies assessing the relationship between early adversity and attentional biases towards threat, or interpretation bias of emotional faces, have done so in those with or without a history of childhood maltreatment. However, the high rates of psychopathology in maltreated children, renders it very difficult to establish a causal effect of maltreatment on the development of these biases. For example, Pine et al. (2005) assessed 34 maltreated and 21 non-maltreated children aged 7-13 using several sources, including case records and a standardised questionnaire assessing domestic violence (Kaufman, 1991), completed by the parents. A computer-based dot-probe task was then used to assess attention bias. The authors reported that maltreated children had an attentional bias away from threatening facial expressions (i.e., attentional avoidance). However, the study also assessed current psychopathology using the Screen for Child Anxiety Related Emotional Disorders (Birmaher et al., 1997), the Child Behaviour Checklist Teacher Report Form (Achenbach, 1991), as well as a full structured psychiatric interview (K-SAD-PL) (Kaufman et al., 1997), and found that 29 of the 34 maltreated participants met the criteria for PTSD. Furthermore, the study found that attention bias away from threatening facial expressions was also associated with PTSD. As a result, the authors were unable to establish whether the cognitive biases were a result of maltreatment or PTSD.

These findings demonstrate that research into the aetiology of cognitive biases should also consider healthy individuals, in order to examine the development of these biases without the potential confounding effects of psychopathology. A small number of studies have taken this approach, assessing the effects of early life stress in healthy children and adults on attention and interpretation biases. For example, Gibb et al (2009) examined the effect of childhood abuse (measured retrospectively using The Childhood Trauma Questionnaire (CTQ; (D. Bernstein & Fink, 1998; D. P. Bernstein et al., 2003)), on both attention and interpretation biases for emotional facial expression in 217 undergraduate students (Gibb, Schofield, & Coles, 2009). Computer based assessments were used to measure both biases. Attention bias was assessed using a modified dot probe task (MacLeod, Mathews, & Tata, 1986) whereby

pairs of facial expression were presented consisting of one emotional (angry, happy and sad) and one neutral face. Interpretation bias for emotional facial expressions were assessed by morphing between a continuum of neutral and emotional faces from a different set of standardised stimuli at 10% increments, creating nine pictures per actor. The results showed that self-reported childhood abuse was associated with both attention bias and interpretation bias for angry facial expressions. Specifically, those who had experienced moderate to severe abuse showed attention allocation towards angry facial expressions but not happy or sad. Furthermore, a history of abuse was associated with an increased propensity to interpret ambiguous facial expressions as angry. That is, when compared to those with no history of abuse, abused participants required a lower level of emotional expression to label a face as angry during the morphing continuum task. While this study replicated findings from studies with similar designs examining attention bias (Pollak & Tolley-Schell, 2003), and interpretation bias (Pollak & Kistler, 2002; Pollak & Sinha, 2002) in children, it was also the first to assess these effects in young adults, or to measure both attention bias and interpretation bias within the same sample.

These studies suggest that individuals who have experienced early life stress may be more likely to attend to threatening information and interpret ambiguous information as threatening, even in the absence of psychopathology. However, there appears to be a distinct lack of research examining the effect of early adversity on memory bias. Furthermore, the majority of studies have focused on rare and particularly severe early life stress, such as childhood maltreatment. Far less is known about the impact of more common and less severe stressful life events on cognitive biases in population samples, with these limited findings often being mixed.

For example, some studies show a correlation between stressful life events and attentional bias measured using a modified emotional Stroop task (MacLeod & Hagan, 1992). However, several studies have failed to replicate these findings (Jenness, Hankin, Young, & Smolen, 2016; Kruijt, Putman, & Van der Does, 2014), possibly as a result of using a different measure (the dot probe task). Nevertheless, positive associations have been reported for other biases including rumination (Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013) and anxiety sensitivity (Zavos, Wong, et al., 2012). A positive correlation between stressful life events and cognitive biases could suggest that they play a potential causal role in the development of cognitive biases. However, an equally plausible explanation is that individuals with negative cognitive biases simply experience more negative life events or interpret events

in a more negative way, leading to a reporting bias. In order to address this issue, Zavos et al. used a longitudinal study sample of over 1,500 individuals assessed at three timepoint at 15, 17, and 20 years of age (Zavos, Wong, et al., 2012). Analyses were conducted separately for independent events and dependent events. Independent events were those that were unlikely to be the result of the individual's behaviour (i.e., the death of a close relative). In contrast, dependent events were those that were more associated with an individual's behaviour (i.e., the breakup of a relationship). The results suggested that child and parent measures of dependent stressful life events were associated with increased levels of anxiety sensitivity both proximally and longitudinally. However, the effects of independent stressful life events were smaller for child measures and non-significant for parent measures. Independent events also only showed proximal associations with anxiety sensitivity, suggesting more of a short-term effect. These findings suggest that the association between stressful life events and anxiety sensitivity may be, at least in part, explained by reverse causality. That is, individuals with higher anxiety sensitivity may be more likely to experience stressful life events. Nevertheless, associations were significant (albeit smaller) for events that were independent of an individual's behaviour suggesting that stressful life events could still play a causal role in anxiety sensitivity.

Taken together, it does seem that environmental factors are associated with several cognitive biases. However, there remain several gaps in the literature. Firstly, the majority of this research has focussed on severe childhood adversity. While some studies show these effects extend to more common stressful life events, findings are mixed. Furthermore, given that many stressful life events are dependent on an individual's behaviour it remains unknown whether any positive associations between stressors and cognitive biases are due to reverse causality. Separate analyses of dependent and independent events may address this issue. However, very few studies have taken this approach. Secondly, while attention bias has been extensively studied, there is a significant lack of research regarding interpretation bias and very few studies of memory bias, or studies that include multiple biases in the same sample. Thirdly, there also seems to be a distinct lack of research examining positive environmental effects on positive or negative cognitive biases. Finally, there remains a lack of understanding regarding the causes of heterogeneity in the effect of adversity, both within and between study samples. One plausible explanation is that this heterogeneity is the result of genetic differences. That is genetic variants influence the effects of adversity on cognitive biases in some individuals but not others.

1.3.3. Gene-environment interplay and cognitive biases

The above research suggests that there are genetic and environmental influences on cognitive biases. However, further studies suggest that these factors do not work in isolation. Rather, that genetic variants moderate the effects of the environment on the development of cognitive biases. Several studies have shown this effect in a number of different candidate genetic variants. For example, one study reported that variation in the 5-HTTLPR moderated the relationship between childhood physical abuse and attention bias for emotional faces (Johnson, Gibb, & McGeary, 2010). In this study 86 women (46 with at least one DSM 4 MDD and 40 with no history of DSM 4 mood disorder) were assessed for attention bias using a computer based modified dot-probe task whereby pairs of stimuli (faces) consisting of one neural face and one affective face (happy, angry, sad) were presented simultaneously. Findings demonstrated that women with one or more S-allele, having experienced physical abuse as a child, (measured using the CTQ (D. Bernstein & Fink, 1998)), had an attentional avoidance bias for angry, but not happy or sad faces. In contrast, physical abuse had little effect on cognitive biases in those homozygous for the L-allele. The interaction between the 5-HTTLPR genotype and physical abuse remained significant after controlling for both past and present depression and anxiety, suggesting that the effect was not confounded by psychopathology.

In a more recent study researchers examined whether the 5-HTTLPR also moderated the effects of recent stressful life events on attention bias measured using the same modified dot-probe paradigm used by Johnson et al. (2010) in 467 children and adolescents (Jenness et al., 2016). Stressful life events were assessed using The Adolescent Life Events Questionnaire (ALEQ: (Hankin & Abramson, 2002)), and participants were asked to identify how many of the 37 items had occurred over the last 3 months. The study found a significant interaction between the 5-HTTLPR and stressful life events on attentional biases. However, the findings contradicted those of Johnson et al. (2010) despite using the same attention bias paradigm. Specifically, in individuals who were homozygote for the S-allele, stressful life events were associated with an attentional bias *towards* rather than away from negative facial expressions (angry and sad). Putting size, age, and gender of the study sample aside, the difference in results may have also been affected by a difference in effect between the more extreme childhood physical abuse and the more common stressful life events, or indeed a recency effect, as the stressful life events reported were confined to the last 3 months.

In another study of the 5-HTTLPR researchers investigated how the effect of emotional abuse in childhood and recent negative life events on attention bias and one's ability to

recognise others' state of mind might be moderated by variation in 5-HTTLPR in a sample of 215 young adults aged between 17-35 (Kruijt et al., 2014). A short version of CTQ (CTQ-SF: (D. P. Bernstein et al., 2003)), and the List of Threatening Experiences Questionnaire (LTE-Q: (T. Brugha, Bebbington, Tennant, & Hurry, 1985; T. S. Brugha & Cragg, 1990)) were used as a retrospective measure of childhood emotional abuse and recent negative life events respectively, with a dot-probe task used to assess attention allocation. No significant interaction was observed between 5-HTTLPR and recent negative life events or childhood emotional abuse on attention bias and these results remained non-significant when taking into account rs25531. However, the recognition of negative states of mind, measured using the Reading the Mind in the Eyes Test (RMET: (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001)), was significantly moderated by the 5-HTTLPR. That is, for those with low expressing genotypes (SS, SLg, LgLg), recent negative life events were associated with an increased ability to recognise negative states of mind but had little effect on those with high expressing genotypes (LL, LaLa). In line with these findings, studies have also identified an interaction between 5-HTTLPR and stressful life events on rumination. Specifically, recent stressful life events (Canli et al., 2006) and emotional abuse in childhood (Antypa & Van der Does, 2010) have been shown to result in increased rumination in individuals with the low expressing S-allele of the 5-HTTLPR, but these environmental factors had little influence in those with high expressing alleles. Significant interactions between 5-HTTLPR and childhood maltreatment on anxiety sensitivity have also been reported (Stein et al., 2008), although these findings failed to replicate in a large (n=1500) 5-year longitudinal study of 15-20 year olds exploring the effects of self-reported stressful life events (Zavos, Wong, et al., 2012).

Very few studies have investigated GxE effects on cognitive biases in further candidate genes. Although there is some evidence of GxE regarding COMT and BDNF. Specifically, Jenness et al. (2016) showed that in those with the COMT Val/Val genotype stressful life events were associated with an attentional bias away from positive facial expressions (happy). In contrast, stressful life events had no effect on attentional bias in individuals with the Val/Met or Met/Met genotypes at this locus. In one of very few studies to assess GxE on memory bias, researchers examined whether variation in BDNF Val66Met (rs6265) had a sex specific effect in moderating childhood stressful life events on memory bias (van Oostrom et al., 2012). The study used the Life Events Questionnaire (T. S. Brugha & Cragg, 1990) to assess childhood stressful life events, and Self-referent encoding task (SRET: (C. Hammen & Zupan, 1984)) to measure participants memory bias. In possibly the only study to assess sex differences in

cognitive biases in a healthy sample, results showed BDNF Val66Met (rs6265) as significantly moderating the effect of childhood stressful life events on memory bias, but only in males. Specifically, childhood stressful life events were associated with a reduced memory bias for positive information but only in males carrying the Met allele. This effect was not found for Val/Val carriers. Whilst this finding could suggest a sex specific effect of BDNF Val66Met (rs6265) on memory bias, it could also reflect sex specific differences in the experience and memory of stressful life events, or the way in which those events are reported.

From the research highlighted above, there is some evidence that specific genetic variants moderate the effects of adversity on cognitive biases. This may explain why the effects of adversity on cognitive biases, or indeed genetic influences, vary so substantially within and between samples given that most studies have failed to take this interaction into account. Nevertheless, GxE research on cognitive biases remains in its infancy. Very few studies have been conducted to date and findings are inconsistent, particularly in research focussing on the 5-HTTLPR and attention bias. Whilst this may be due to a lack of reliability regarding the measure of attention bias, it may also reflect a latent effect regarding individual differences in how life events and childhood adversities are processed, as discussed earlier. Furthermore, very little GxE research has been conducted on memory bias, and no studies have explored GxE effects on interpretation bias or explored multiple biases in the same sample. In addition, GxE studies of cognitive biases have largely been limited to 5-HTTLPR and studies are yet to explore other variants implicated in environmental sensitivity (the ability to register, process, and respond to environmental conditions) or the cumulative effect of these variants. Lastly, although there has been much research focus on specific variants moderating the effect of negative life events on negative cognitive biases, very little research has considered whether genetic variants also moderate the effect of positive life events on positive cognitive biases. It has been suggested that variants implicated in environmental sensitivity could operate in such a way as to promote adaptive functioning in response to positive environments (Fox & Beevers, 2016), similar to the same variants moderating the effect of negative environments on negative outcome.

1.3.4. Cognitive biases, depression and anxiety: A shared genetic architecture

Twin studies suggest that cognitive biases are heritable (Eley et al., 2007; Eley et al., 2008; Rijsdijk et al., 2009) and have shown evidence for genetic overlap with both depression (Eley et al., 2008) and anxiety (Eley et al., 2007; Eley et al., 2008). However, to date there have

been very few molecular genetic studies of cognitive biases. Despite this deficit, the few studies that have been conducted suggest that the same genetic variants that have been shown to moderate the effects of adversity on the development of depression and anxiety, also influence cognitive biases. For example, in the first study of its kind, allelic variation in 5-HTTLPR was also assessed for its association with both positive and negative attention biases using a dot probe paradigm that presented 20 positive valanced images, 20 negative valanced images and 40 neutral images (Fox, Ridgewell, & Ashwin, 2009). There was a significant interaction between the 5-HTTLPR and the emotional valence of the images on reaction time in the task. This suggested that the L-allele homozygotes of 5-HTTLPR showed increased vigilance for positive stimuli and increased avoidance of negative stimuli when compared to carriers of the S-allele (SS and LS). This finding was partially supported by a later meta-analysis that also examined the A/G SNP rs25531 that occurs inside the LPR and requires additional genotyping steps to capture (Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012). This meta-analysis found that individuals' carrying the low expression genotype of 5-HTTLPR (S/S, S/L_G, L_G/L_G) exhibited an attentional bias towards negatively valanced stimuli which was not observed in those with the intermediate (S/L_A, L_A/L_G) or high (L_A/L_A) expression genotypes. Furthermore, research has also extended findings regarding a link between 5-HTTLPR and attention bias by demonstrating that variation in the same variant are also associated with interpretation biases for emotionally ambiguous information (Fox & Standage, 2012). The study, which also assessed the A/G SNP rs25531, used a verbally presented list of 56-word consisting of 28 unambiguous neutral words, 14 unambiguous threat-related words, and 14 homophones with both neutral and threat-related meaning (e.g. Die/Dye) (Mathews, Richards, & Eysenck, 1989). Results, in line with previous research of the same variant and attention bias, demonstrated that those with low expression (S/S, L_G/L_G, or S/L_G) genotypes of the LPR interpreted homophone words as threatening significantly more so than those with the high expression (L_A/L_A) of the same variant.

In addition to the 5-HTTLPR, a small number of further genetic markers implicated in GxE studies of depression and anxiety have also been assessed for associations with cognitive biases. In a study assessing the effects of COMT Val158Met (rs4680) and DRD2 (rs1800497) on attention bias for emotional facial expression using the spatial cueing task it was demonstrated that whilst variation in COMT Val158Met (rs4680) was significantly associated with a negative attention bias, variation in DRD2 (rs1800497) were conversely associated with a positive attention bias (Gong et al., 2013). Specifically, COMT Met carriers, compared to

Val/Val carrier, attended to negative facial expression, while DRD2 (rs1800497) T allele carriers were shown to attend more to positive facial expressions. This study is part of only a small group to have assessed genetic effect on both positive and negative attention bias. Furthermore, the sample consisted of 650 college students making it relatively powerful to detect accurate effects. In another study assessing the differential effects of FKBP5 (rs1360780) on attention bias using the dot probe task, researchers found that T allele carriers showed a heightened attention bias for threat when compared to individuals' homozygous for the C allele (Fani et al., 2013). Moving away from attention bias, a study examining the effects of variations in BDNF Val66Met (rs6265) and 5-HTTLPR on rumination (a focus on negative thoughts and feeling related to the self), whilst finding no association between the LPR and rumination, did so with variation in BDNF Val66Met (rs6265) (Beevers, Wells, & McGeary, 2009). The study, conducted on healthy adults, found that Val/Met heterozygotes had a significantly higher likelihood of ruminating than the Val/Val carriers. However, it is important to highlight that rumination was assessed using the 10-item self-report ruminative response scale, and responses may therefore have been impacted by the participants mood or pre-existing bias. Additionally, the study may have also been underpowered as it only assessed a total of 71 individual, with only 10 items by which to measure rumination. This in turn may have resulted in false positives. However, despite some limitations, the findings of these studies serve to highlight the shared genetic architecture of psychopathologies such as depression and anxiety and cognitive biases.

1.3.5. Cognitive biases as potential intermediate phenotypes for psychopathology and targets for interventions and treatments

Research presented thus far has demonstrated that cognitive biases are heritable (Eley et al., 2007; Eley et al., 2008; Lau & Eley, 2008; Lau et al., 2006; Rijsdijk et al., 2009), with research also highlighting a shared genetic architecture between cognitive biases and both depression (Eley et al., 2008) and anxiety (Eley et al., 2007; Eley et al., 2008). Additionally, research has also suggested that in the presence of stressful life events, cognitive biases *can* lead to the development, maintenance, and recurrence of psychopathologies such as depression and anxiety (A. T. Beck & Clark, 1997; Ingram, 1984; LeMoult & Gotlib, 2019; Muris & Field, 2008; Teasdale, 1988). This suggests that biases in cognition are not state dependant, meaning that a diagnosis of depression or anxiety, or being in a depressive or anxious state is not required to exhibit a cognitive bias. Lastly, biases in cognition are relatively reliable and easy

to measure, strongly correlate with normal variations in personality traits, and can be linked to emotional resilience and vulnerability (Fox et al., 2009). This collective evidence suggests that cognitive biases may indeed represent potential intermediate phenotypes for both depression and anxiety. Such biases could therefore help explain the differential interpretation, experience and effects of environmental factors across individuals and improve our understanding of how psychopathologies such as depression and anxiety begin to develop. It may well be that genetic risk for both depression and anxiety manifest as biases in cognitive processing, which in time can lead to symptoms of psychopathology, affectively mediating the genetic risk.

Although limited in number, there have been research efforts to assess whether cognitive biases mediate genetic influences on depression and anxiety in children and adolescents. For example, Lau and Eley (2008) examined the effects of attributional style as a potential risk marker for depression in a sample of approximately 2,500 adolescent twins and siblings across two timepoints. Findings from a cross-lagged mediation model demonstrated a reciprocal relationship between attribution style and depression symptoms with bidirectional effects between the two that were longitudinally consistent. Negative attribution style occurred before, during and after symptoms of depression, with attribution style itself showing moderate heritability at both timepoints, ranging from 28% at timepoint one and 23% at timepoint two for younger adolescents, and 38% at timepoint one and 40% at timepoint two for older adolescents. Findings also highlighted genetic associations regarding attribution style and symptoms of depression both within and across timepoints, with the strongest associations amongst older adolescents and females, as well as those reporting increased numbers of independent negative life events. The authors also noted that due to the "interlocking" association between depression and attribution style, a finding that could indicate attribution style as state dependent, it was difficult to discern the chronicity of their appearance. This suggests the need to examine the association during the principle emergence of attribution style at an earlier period of development (Turner & Cole, 1994), when symptoms of depression are lower (Ford, Goodman, & Meltzer, 2003).

One particular challenge regarding this type of research is attempting to disentangle issues surrounding reverse causality whereby the outcome variable maybe driving the development of the mediating variable, or when there is evidence for a reciprocal relationship whereby the two variable feed each other's development and maintenance. This was evident in the study by Lau and Eley (2008), as discussed above. Another challenge here is to examine how life events may moderate this relationship, an important issue that was also examined in

the study by Lau and Eley (2008). They noted that the older male individuals within the sample who had experienced a greater number of independent negative life events were also shown to have the highest genetic effect on both symptoms of depression and attribution style. Conversely, younger female participants within the sample demonstrated increased shared environmental effects regarding these measures.

Further studies examining, in particular, the effect of cognitive biases as mediators between genetic risk and an outcome of psychopathology are few. However, studies have examined anxiety sensitivity (containing elements of both attention and interpretation bias) in relation to panic/somatic ratings (Eley et al., 2007) and depression and anxiety (Zavos, Rijsdijk, et al., 2012) in samples of 300 twin pairs and 1,300 twins and siblings respectively. In the former, researchers found a substantial genetic correlation between anxiety sensitivity and panic/somatic ratings, whilst in the latter it was noted that the relationship between depression and anxiety may be influenced by anxiety sensitivity overtime. Whilst neither study had sufficient data to examine whether anxiety sensitivity mediated these relationships the authors both called for further research to examine whether the genetic risk for panic disorder (an anxiety subtype), and the relationship between depression and anxiety might be mediated by anxiety sensitivity. More recently, studies have attempted to test mediators of polygenic risk using genome-wide data. In a study by Navrady et al. (2018), the relationship between genetic risk for depression and both self-reported and clinical depression was found to be independently mediated by both neuroticism (43–57%) and in the opposing direction resilience (37–40%), in a population based cohort of 4,166 individuals. However, whilst this study did include related phenotypes such as neuroticism and resilience, no study to date using this approach has considered cognitive biases as a mediator.

1.3.6. The CogBIAS Hypothesis

In a recent hypothesis put forwards by Fox and Beevers (2016), they suggest that cognitive biases may represent a potential mechanism responsible in part for Differential Susceptibility. The CogBIAS hypothesis (Fox & Beevers, 2016), outlines a theoretical framework describing how both genetic and environmental factors co-act in the development of both negative ('toxic') or positive ('enhancing') cognitive biases and how these later lead to psychopathology or wellbeing respectively (see **Figure 1.1**).

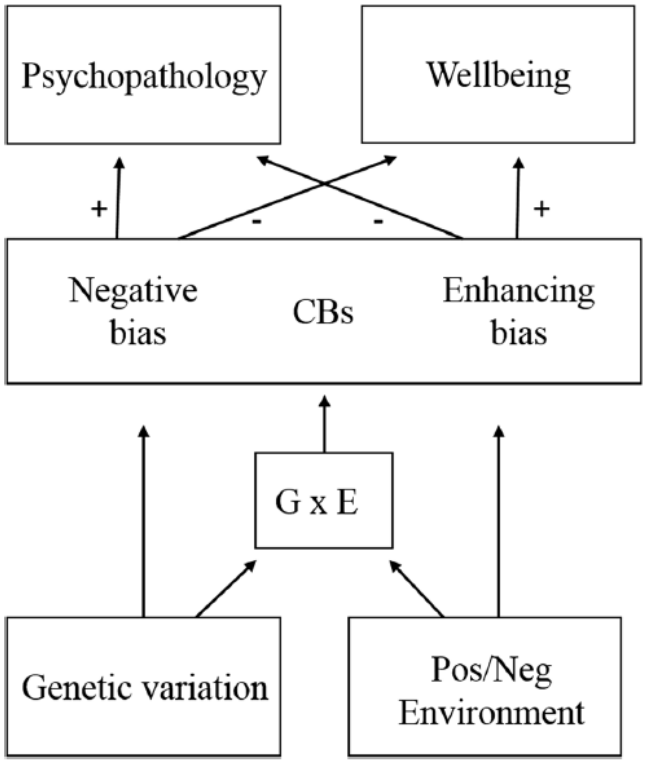


Figure 1.1. The CogBIAS hypothesis illustrating how gene-by-environment interaction (GxE) leading to negative and enhancing cognitive biases (CBs) could potentially mediate genetic and environmental effects on psychological functioning (wellbeing and psychopathology).

The CogBIAS hypothesis proposes that negative and positive cognitive biases operate as mechanisms that mediate the pathway between genetic and environmental factors and psychological functioning. Specifically, the model suggests that genetic variants that increase sensitivity to negative environments lead to the development of negative ('toxic') biases but only in the context of adversity. In contrast, genetic variants that increase sensitivity to positive environments lead to a positive ('enhancing') cognitive bias, but only in the context of a positive environment. Finally, genetic variants that increase sensitivity to both negative and positive environments (environmental-sensitivity genes) may lead to either negative or positive biases depending on the environmental context. Once established, these biases can lead to either advantageous (wellbeing) or detrimental (psychopathology) outcomes, depending on the environmental context. For example, while a negative cognitive bias would increase risk of psychopathology and decrease likelihood of wellbeing, an enhancing cognitive bias would likely increase wellbeing and reduce risk of psychopathology (Booth et al., 2017).

A study by Fox et al. (2011), which eventually lead to the development of the CogBIAS hypothesis, has demonstrated differential effects of an environmental intervention designed to modify attention bias across two distinct genotypic groups. The study assessed 116 participants

with high (La/La) and low (S/S, S/Lg, and Lg/Lg) expression genotypes of 5-HTTLPR. Each participant was randomly allocated into one of two groups that either training attention towards negative material or towards positive material using a standard computer-based attention bias medication (ABM) procedure. Findings demonstrated that carriers of the low expression form of 5-HTTLPR developed a stronger negative *and* positive attention bias for affective pictures when compared to those with the high expression form. This was the first time that allelic variations in the promoter region of 5-HTTLPR had been shown to be associated with differences in sensitivity to an ABM procedure, highlighting the potential for a cognitive mechanism regarding past GxE interactions involving this variant.

However, whilst this and other studies discussed throughout this chapter do provide some support for elements of the CogBIAS hypothesis, there remains a substantial gap between the research evidence and the proposed effects highlighted in the CogBIAS model. Firstly, whilst several experimental studies, discussed above have demonstrated associations between attention bias and stress response there is yet to be a study assessing the effects of cognitive biases longitudinally, in the context of daily life events. Studies using experience sampling methods (ESM), a structured diary technique that assesses subjective experiences in daily life, have demonstrated the effects of personality traits (Komulainen et al., 2014) and sensitivity to punishment and reward (Hundt et al., 2013) in response to daily life on levels of positive and negative affect. However, to date, this approach is yet to be used to assess the effects of positive and negative cognitive biases on such outcomes. The benefits of using such an intensive longitudinal method, such as ESM, is that it can unravel temporal processes (both descriptively and through causal analysis), through substantial repeat measures. This method also provides accurate, in the moment data regarding response to daily life events, avoiding confounding effects of retrospective recall bias and mood congruent effects and is therefore highly ecologically valid. This would provide an ideal platform for assessing the effect of cognitive biases, in an ecologically valid setting, on affective states which have for some time been shown to be associated with both depression and anxiety (Watson, Clark, & Carey, 1988). Furthermore, taking such an approach would allow the effects of cognitive biases to be assessed in a *healthy* population sample without the confounding effects of psychopathology that have often been present in past research. Secondly, most supporting evidence thus far, regarding the effect of genetic and environmental influences on cognitive biases comes from a small amount of twin studies and cross-sectional studies of single genetic variants such as 5-HTTLPR, and a single cognitive bias, with very little attention paid to the role of positive environmental factors.

Therefore, in order to comprehensively test the CogBIAS hypothesis it is necessary to explore the effects of positive and negative environments on a range of positive and negative cognitive biases and assess whether variants that increase sensitivity to the environment moderate environmental effects on cognitive biases. Thirdly, whilst there have been a handful of longitudinal twin studies suggesting that cognitive biases do mediate genetic risk for depression and anxiety on later depression and anxiety symptoms, there has been no research attention pursuing this using a molecular genetics approach. To further test the assumptions of the CogBIAS hypothesis it will also be necessary to examine whether cognitive biases mediate genetic risk for psychopathology on symptoms of depression and anxiety at later timepoints.

1.4. Aims and Hypothesis.

The current thesis aims to test the original CogBIAS hypothesis across three separate study chapters examining the development and potential causal effects of multiple cognitive biases on affective states and disorders such as depression and anxiety. The CogBIAS hypothesis will be assessed in three separate parts, represented by each study chapter. Study one (Chapter Three) will focus on the effect of cognitive biases throughout the course of daily life. Study two (Chapter Four) will use genetic and environmental data to examine the developmental aetiology of cognitive biases. Study three (Chapter Five) will examine genome-wide associations between cognitive biases and psychopathologies depression and anxiety, and the mediating effect of cognitive biases.

1.4.1. Chapter three: Study One: An ESM approach

The initial premise of the CogBIAS hypothesis is that an established 'enhancing' or 'toxic' cognitive bias may result in further information processing being skewed, promoting sensitivity to environmental effects, and impacting on affective states. To date, only a handful of studies have examined the effect of cognitive biases on affective mood states (Clasen, Wells, Ellis, & Beevers, 2013; Fox, Cahill, & Zougkou, 2010; LeMoult, Arditte, D'Avanzato, & Joormann, 2013), often demonstrating a significant effect of cognitive biases on negative mood following experimentally induced stress. However, no studies have assessed these effects in daily life despite these, and the findings of other studies, suggesting that cognitive biases may be instrumental, not just for the development and maintenance of negative affective moods, but also for disorders such as depression and anxiety (A. T. Beck & Clark, 1997; Ingram, 1984; LeMoult & Gotlib, 2019; Muris & Field, 2008; Teasdale, 1988).

In study one (Chapter Three), an ESM approach will be taken to assess the relationship between cognitive biases in attention, interpretation and memory and response to events in daily life on positive and negative affect. This approach is expected to show significant effects of cognitive biases measured at baseline on daily levels of affect directly and through interaction with environmental contexts. This is intended to demonstrate, in support of the CogBIAS hypothesis, that variations in cognitive biases are associated with levels of positive and negative affect, and therefore also resiliency and vulnerability to psychopathology (see **Figure 1.2**).

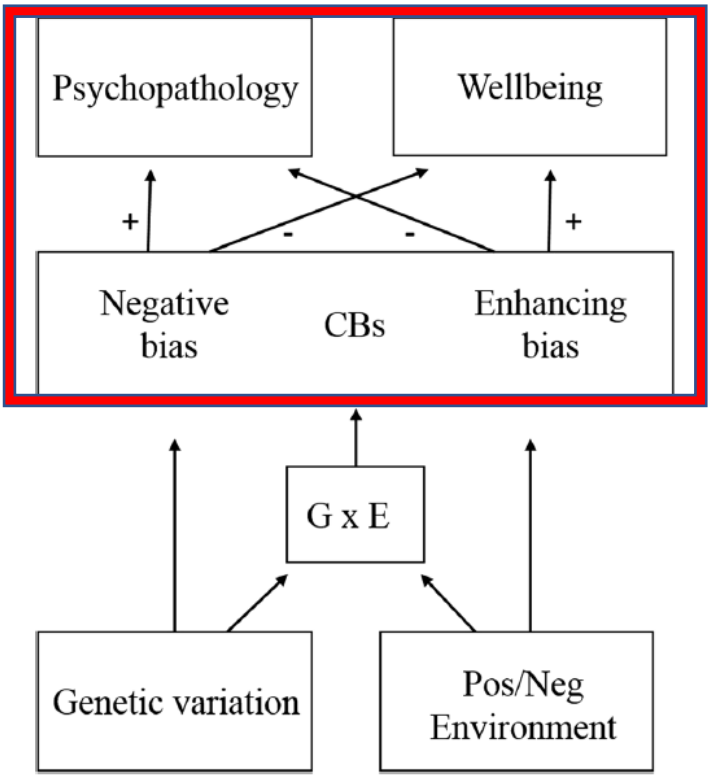


Figure 1.2. The CogBIAS model as originally proposed by Fox and Beavers (2016). The red box illustrates what specific aspects of the CogBIAS hypothesis were tested study one.

1.4.2. Chapter four: Study two: A Candidate gene approach

The CogBIAS hypothesis proposes that cognitive biases arise as a result of both genetic variation and environmental effect as well as the interplay between them. Specifically, that genetic variants shown to increase sensitivity to environmental effects may result in the development of a positive or negative bias depending on the environmental quality. Whilst there have been several studies examining the effect of candidate genetic variants on cognitive biases most have focused on the much-researched serotonin transporter 5-HTTLPR (Beevers et al., 2009; Fox et al., 2009; Fox & Standage, 2012; Fox et al., 2011), with a small number of

further studies examining association with COMT (Gong et al., 2013), DRD2 (Gong et al., 2013), BDNF (Beevers et al., 2009) and FKBP5 (Fani et al., 2013). However, the main caveat with these studies is that they have tended to be cross-sectional in design and assess a single variant and single cognitive bias, most notably attention bias.

Using pre-existing longitudinal data, study two (Chapter Four) will assess multiple genetic variants previously implicated in GxE research of depression and anxiety, and their effect on the development of cognitive biases in attention, interpretation and memory at three timepoints, across four years. This will include assessing GxE effects regarding positive and negative life events to assess the moderating effects of specific genotypes on these cognitive biases. This is expected to demonstrate, in further support of the CogBIAS hypothesis, that selected sensitivity genes and life events have significant effect on the development of cognitive biases both through their independent main effect and interactions (see **Figure 1.3**).

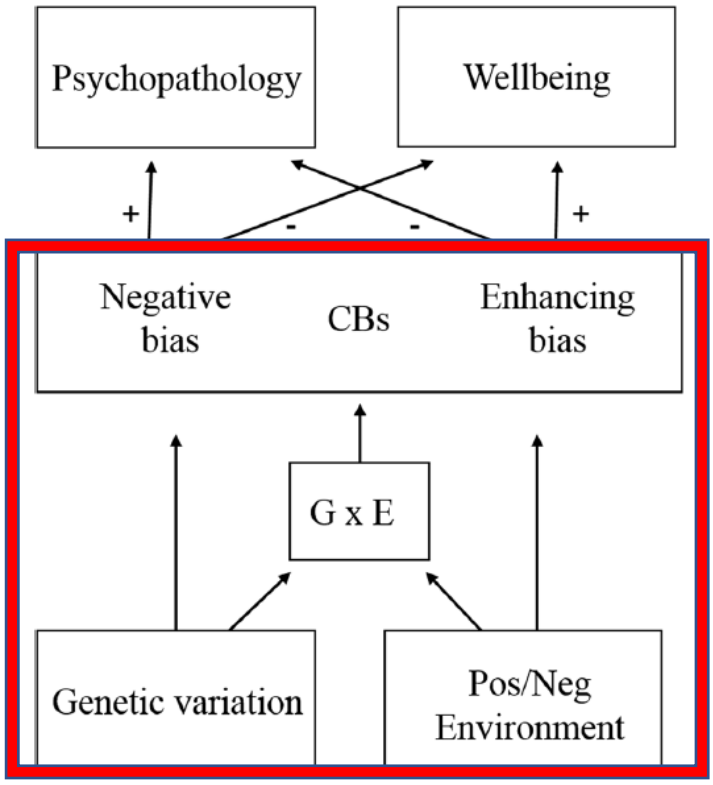


Figure 1.3. The CogBIAS model as originally proposed by Fox and Beavers (2016). The red box illustrates what specific aspects of the CogBIAS hypothesis were tested study two

1.4.3. Chapter five: Study Three: A Phenome-wide approach

The CogBIAS hypothesis also proposes that once a negative or positive cognitive bias is in place, the resulting skewed information processing will eventually lead to either

psychopathologies such as depression or anxiety, or enhanced levels of wellbeing respectively. This has important implications if found to be the case as targeting such cognitive processes would likely improve the efficacy of behavioural treatments and interventions and aid in the development of novel approaches to preventing affective disorders such as depression and anxiety. Previous research examining the mediating effects of cognitive biases are limited (Lau & Eley, 2008), with no studies to date examining such mediation using genome-wide data during developmentally sensitivity periods such as childhood and adolescences.

Extending on the previous effects explored in study two, study three (Chapter Five) will take a phenome-wide polygenic approach to explore associations between cognitive biases, genetic risk for depression, and depression and anxiety symptoms. Following this, the mediation of genetic risk for depression by cognitive biases at specific timepoints on later depression and anxiety symptoms will be assessed. This approach is expected to demonstrate, in keeping with the expectations of the CogBIAS hypothesis, that cognitive biases are important mediators of risk for affective disorders and represent targets for novel treatment and intervention strategies (see **Figure 1.4**).

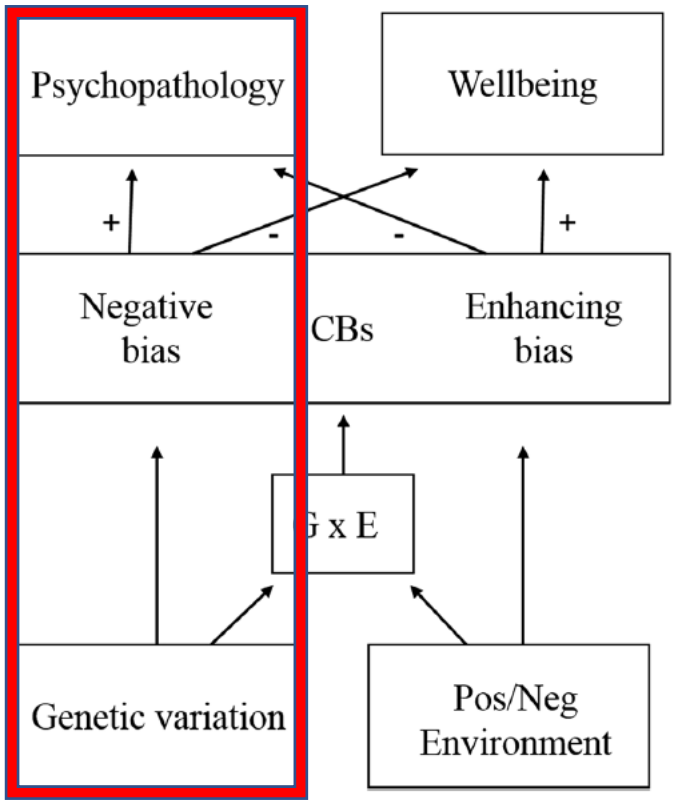


Figure 1.4. The CogBIAS model as originally proposed by Fox and Beavers (2016). The red box illustrates what specific aspects of the CogBIAS hypothesis were tested study three.

2. Chapter 2 – Methods

*N.B. This chapter contains information adapted for the following publications:

Booth, C., Songco, A., Parsons, S., Heathcote, L., **Vincent, J**., Keers, R. and Fox, E., 2017. The CogBIAS longitudinal study protocol: Cognitive and genetic factors influencing psychological functioning in adolescence. *BMC Psychology*, 5(1), p.41.

The three empirical chapters within the current thesis reflect work conducted as part of two separate studies, each of which utilise two distinct samples. The first of these studies, the *Cognition and Response to Environmental Stimulus* (CRESt) study, consists of primary data collected by the author and is the basis for work conducted towards Chapter three in the current thesis. The fourth and fifth chapters are based on work conducted as part of the *CogBIAS longitudinal study* (CogBIAS-L-S: (Booth et al., 2017)). This chapter will give an in-depth description of the methodologies and research instruments used across the CRESt study and CogBIAS-L-S with further detail provided, when necessary, regarding particular elements relevant to this thesis.

2.1. Study One (Cognition and Response to Environmental Stimulus (CRESt) - The effect of cognitive biases on affective states in response to daily life events)

2.1.1. Design

The CRESt study was designed to assess short-term changes in mood state in relation to cognitive biases in attention, interpretation and memory throughout the course of daily life. After baseline assessments of cognitive biases, which took place in laboratory settings at Queen Mary University of London (QMUL), each participant completed seven days of experience sampling which assessed moment-to-moment mood states in association with daily contextual environments. To examine each participant's moment-to-moment mood states, and information regarding the environmental contexts their momentary experiences were recorded over the course of seven days. This was achieved using a fully customisable ESM smartphone application called LifeData, which was adapted in house at QMUL for the purpose of the current study.

2.1.2. Sample

Recruitment for the CRESt study resulted in 100 participants aged between 18-30, with a mean age of 22.55 (it was not possible to collect more data due to time and financial constraints). However, following quality control 26 individuals were dropped from the sample due to unsatisfactory data regarding the cognitive assessments and/or the seven days of experience sampling, leaving a final sample of 74 participant (12 males, 62 females), with ages ranging from 18-30 and a mean age of 22.51. Specific reasons for participant exclusion are given below in **Section 2.1.5**.

Participants were recruited from several universities across London, including Queen Mary University of London, Kings College London and Goldsmiths University of London, as well as from the general population living in London at the time of the study. Advertisements calling for CRESt study participants were posted on all above-mentioned London university websites and were also included in monthly university newsletters. Further advertisements were posted online using platforms such as reddit.

Inclusion criteria was limited to potential participants being between 18-30 years of age and free of any current or previous clinically diagnosed psychopathology. All participants that took part in the study were paid £50 worth of "Love to Shop vouchers".

2.1.3. Ethics

Ethical approval for the CRESt study was obtained from the QMUL ethics committee (QMREC1508). The project also received consent from QMUL, Kings College London and Goldsmith University of London to advertise for participants within each respective universities' monthly newsletters. Verbal and written consent regarding participation in the study, and the use of their data was also obtained from each participant on the day of cognitive bias testing at QMUL. A debriefing document was also sent via email to each participant at the end of their experience sampling period further explaining the nature of the study, and how their ESM data would be used alongside their cognitive bias data. This document also included contact details of the lead investigator in the case of any further question regarding the study, or if they wished for their data to be removed from the study entirely.

2.1.4. Procedure

All baseline cognitive bias testing was conducted at QMUL. Potential participants indicated their availability on an online calendar before coming to QMUL for computerised cognitive assessments designed to assess attention, interpretation and memory biases across three separate tasks as described below. Upon arrival participants were met by a member of the research team and taken to a testing room. Following a brief set of instructions regarding the assessment each participant completed each of the three computerized cognitive tests consecutively. Following cognitive testing participants were shown how to install the ESM smartphone application on their own phone that would assess daily environmental contexts and levels of positive and negative affect over seven days as highlighted below in **Table 2.1**, and discussed in detail in the following section. After installing the ESM application participants were given a brief tutorial, asked to keep their smartphones with them at all times, and to respond to as many notifications as possible for a total of seven days. Contact details were also given to each participant in the event of any issues regarding the ESM Application. Each participant was then given £50 in "LoveToShop" vouchers as incentive following the cognitive testing.

Table 2. 1: Testing procedure for CRESt study.

Assessments at baseline	**ESM measures over seven-day period**
Cognitive Biases:	*Context:*
Dot-probe task (Attention bias)	Quality of previous event
Scrambled Sentence Task (Interpretation bias)	Quality of current activity
Self-Referential Encoding Task (Memory bias)	Quality of solitude (if alone)
	Quality of social interaction (if not alone)
	Positive Affect:
	How enthusiastic / cheerful / relaxed / content / safe do you feel right now?
	Negative Affect:
	How worried / tense / down / lonely / guilty do you feel right now?

2.1.5. Measures

2.1.5.1.Attention Bias

A modified pictorial *dot-probe task* (MacLeod et al., 1986), using images selected from the International Affective Picture System (IAPS: (P. Lang, Bradley, & Cuthbert, 2008)), was used to obtain a measure of each participants' attention bias. This computer-based task presented participants with a set of 60 positive and 60 negative pictures, which were each displayed independently following a 1x1cm fixation point which appeared for 500 milliseconds (ms) at the centre of the screen. Pairs of pictures, both 7x9cm in size, were presented 6.5cm to the left and right of the centre of the screen for a total of 1000ms. Each pair of pictures were emotionally valanced as either positive vs neutral or negative vs neutral and were followed by a probe (— or |) either behind the emotional valanced image (congruent trial) or the neutral image (incongruent trial) for 3000ms. The probe lines axis changed randomly in order to encourage attention and ensure engagement with the task. As the probe appeared, participants were required to indicate the axis of the probe line as quickly as possible using either the left or right mouse button, with their reaction times measured for each response. Trials consisted of positive vs neutral, negative vs neutral and positive vs negative comprising three trial types in total. The location of the emotionally valanced images, neutral images and probe, including its axis were counterbalanced in all trials with 240 trials in total. At the beginning of the task participants complete 25 practice trials which were excluded from the final measure. Incorrect responses regarding the axis of the probe line and response slower than 2000ms or faster than 100ms were excluded, as were individual outliers more than three standard deviations from the mean. Only participants who had provided valid data for at least 80% of the task were included in downstream analysis. To create a score for negative vs neutral pictures (*negative attention bias*), mean reaction times were calculated for the following conditions: Probe presented on the right and negative emotional picture presented on the left (RpLe_mean); Probe presented on the right and negative emotional picture presented on the right (RpRe_mean); Probe presented on the left and negative emotional picture presented on the right (LpRe_mean; Probe presented on the left and negative emotional picture presented on the left (LpLe_mean). An negative attentional bias scores was then calculated using the formula provided by (MacLeod & Mathews, 1988): 0.5 * (RpLe_mean – RpRe_mean) + (LpRe_mean – LpLe_mean). The same method was used to calculate attentional bias scores for positive vs neutral stimuli (*positive attention bias*) and positive vs negative stimuli (overall *attention bias*). Primary assessments focused on the overall *attention bias* score. However, in the case of a significant

finding further analysis was conducted examining both the positive and negative bias components (*positive attention bias* and *negative attention bias*) separately.

2.1.5.2.Interpretation Bias

The Scrambled Sentence Task (SST: (Wenzlaff, 1991)) was used to measure interpretation bias. The task consisted of a single phase whereby participants were instructed to create a coherent five-word sentence using six words presented to them in an incoherent order. In each instance it was possible to create either a positive or negative sentence (e.g. "life ruining my am improving I" = I am ruining/improving my life). Participants were presented with twenty scrambled sentences and were asked not to deviate from the first sentence that came to mind. Only those participants who had provided ≥14 correct positive or negative sentences were included in downstream analysis. A *positive interpretation bias* score was calculated as the total amount of correct positive sentences provided, and a *negative interpretation bias* score as the total amount of correct negative sentences provided. An overall *interpretation bias* score was than calculated as: (total negative – total positive) / total correct. This resulted in a positive score indicating a more negative interpretation bias, and a negative score indicating a more positive interpretation bias. Again, the primary focus of analysis was on the assessment of the overall *interpretation bias* score. However, when a significant finding was observed further analyses regarding both the positive and negative bias components (*positive interpretation bias* and *negative interpretation bias*) was conducted separately.

2.1.5.3. *Memory Biases*

The Self-Referential Encoding Task (SRET: (C. Hammen & Zupan, 1984)) was used to measure memory bias. The task comprised 3 phases – An encoding phase, a distraction phase, and a free recall phase. During the encoding phase self-referent adjectives were displayed on the screen with the caption "visualize yourself in a scenario with this word". Participants were then required to indicate on a 7-point Likert scale how well they could visualize themselves in a scene with the word. A new word was then presented after a response was given. The word list was comprised of 22 positive (cheerful, attractive, victorious) and 22 negative (scared, unhappy, failure) words and was followed by the distraction phase. The distraction phase instructed participants to indicate how much they liked an array of symbols and signs that were presented to them one at a time. Participants indicated what score they gave each sign on a 10-point Likert scale using the mouse. The final phase was the free recall phase

where participants were instructed to type as many words as they could remember from the encoding phase, regardless of whether they endorsed the word or not. Recalled words were only counted if they were spelt correctly, except in the case of "humour" / "humor" which was accepted in the English or American spelling. Words could be recalled in no specific order. However, any participants who failed to recall any words from the encoding phase were removed from downstream analysis. A *positive memory bias* score was calculated as the total number of positive words that were both endorsed and recalled, with a *negative memory bias* score calculated as the total number of negative words both endorsed and recalled (Asarnow, Thompson, Joormann, & Gotlib, 2014). A *memory bias* score was then calculated as: (negative endorsed and recalled – positive endorsed and recalled) / total endorsed and recalled. Consequently, a positive score indicated a more negative memory bias, and a negative score indicated a more positive memory bias. Once again, the primary focus of analysis was on the assessment of the overall *memory bias* score, with further analysis conducted on both the positive and negative bias components (*positive memory bias* and *negative memory bias*) separately, if a significant finding was observed.

2.1.5.4.Context and affect

A specifically designed ESM smartphone application was used to obtain repeat measures of both environmental contexts and levels of positive and negative affect over a seven-day period. Once installed and activated participants began receiving notifications. Each participant was required to respond to eight notifications per day. They were permitted a 10-minute time lapse between notification and response to ensure that the assessments were in real time, after which the session would expire and be marked as missed. All 'notifications per day' took place between 10.30am and 10.30pm and were at semi-random time points within this daily window. At each notification the participants smartphone would prompt them to answer a series of multiple-choice and short answer questions regarding current emotions, activities, social context and significant events since the last beep. Participants were able to answer all questions using the touch screen of their smartphone. As with previous ESM research, participants included in the data set were required to have a response rate of at least one in three notifications as this has been demonstrated as a valid cut-off for reliability (Komulainen et al., 2014).

Upon each notification participants were first prompted to report how pleasant or unpleasant the most important event was since the last notification ("Think about the most

important event you experienced since the last beep. How pleasant or unpleasant was it?"), indicated on a 7-point Likert scale (1=very unpleasant, 7=very pleasant). This formed a measure regarding the "Quality of previous event". Following this, participants were prompted to answer a question regarding the level of enjoyment they had experienced in terms of their most recent activity ("Think about what you were doing just before the beep. Do you enjoy this activity?"). Participants were then presented with a follow up question probing how well they felt they could perform this activity, answered again with the use of a 7-point Likert scale ("Can you do this activity well?", 1=Not at all, 7=very much so). Responses to both these questions were summed to create a measure regarding the "Quality of current activity". The last context related questions were concerned with who the participant was currently with ("Are you alone right now?", binary "YES" or "NO"). If "YES", participants were prompted to indicate whether they were alone by choice ("Are you alone by choice?", binary "YES" or "NO"). This formed a measure regarding the "Quality of solitude". However, if "NO" participants were asked to indicate, whether they wanted to be alone ("Would you prefer to be alone?", binary "YES" or "NO"). This formed a measure regarding the "Quality of social interaction". All questions were adapted from a previous study by Komulainen et al. (2014).

To assess momentary states of affect participants were also prompted to answer 11 questions at every notification, each centred around words relating to either positive affect (PA) or negative affect (NA). NA words included worried, tense, down, lonely, guilty, stressed (e.g., "How worried do you feel right now?", 1=Not at all, 7=Very much so). Questions relating to PA included the words enthusiastic, cheerful, relaxed, content, safe (e.g. "How enthusiastic do you feel right now?", 1=Not at all, 7=Very much so). Both PA and NA words were selected and adapted from a studies by Hartmann et al. (2015), as well as from the positive and negative affect scale (PANAS: (Watson, Clark, & Tellegen, 1988)). The word stressed was modified from the PANAS item 'distressed' as it was more understandable in the context of the study, and as stress was not being assessed as an outcome of interest. As with previous studies, the standard deviation of each affect was used as a measure of affect variability (N. Jacobs et al., 2011; Komulainen et al., 2014; McConville & Cooper, 1998).

2.2. Study Two (The development of cognitive biases: The effect of candidate "sensitivity" variants, and positive and negative life events)

2.2.1. Design

Study two (Chapter four) and study three (Chapter five) were both designed alongside the CogBIAS Longitudinal Study (CogBIAS-L-S) to longitudinally assess a large cohort of adolescents over a four-year period, with repeated measures taken at three developmentally sensitive time points. The design of the CogBIAS-L-S itself is focused on the assessment of a wide range of both cognitive and subjective factors during a narrow window of development. Participants were tested at 12, 14, and 16 years of age, assessing cognitive biases in attention, interpretation and memory, as well as both positive and negative life experiences and several subjective measures that included both depression and anxiety at each of these time points. Using this approach, the CogBIAS-L-S aimed to identify psychological and genetic factors associated with emotional vulnerability and resiliency, providing insight into risk and protective effects of these factors that may hold particular significance for the design and implementation of strategies aimed at improving psychological functioning. In Chapters four and five of the current thesis specific approaches are taken to examine and test the specific elements of the CogBIAS Hypothesis (Fox & Beevers, 2016).

Study two (Chapter four) was designed as part of the CogBIAS-L-S to examine a specific aspect of the CogBIAS hypothesis: it aimed to assess the development of cognitive biases in attention, memory, and interpretation across three timepoints with a focus on genes, environments (positive and negative life events), and gene-by-environment interactions (GxE). The effect of positive and negative life events on cognitive biases, and their positive and negative components, were separately assessed both across time and by-time. A candidate gene approach was then applied to assess a specific set of 28 systematically selected candidate variants that have been implicated to increase sensitivity to environmental influences in previous GxE studies of depression and anxiety. Using 23 of these candidate variants a candidate sensitivity score (CSS) was created to examine their combined effect on the development of cognitive biases and their positive and negative component. These effects were examined across time and through interaction with time, as well as through interactions with both negative and positive life events. The individual effect of each of the 28 variants were also assessed using the same approaches.

2.2.2. Sample

The CogBIAS-L-S sample consisted of 504 11-12-year-old school children (226 males, 278 females) from a variety of both private and comprehensive schools in Southern England. Whilst the majority of the sample were White Europeans (74.33%), the sample also included Asians (12.22%), Africans or Caribbeans (2.67%), those of mixed ancestry (6.16%) and others (3.49%). However, due to missing data regarding the cognitive bias measures the sample at wave one was reduced to 99.41% of the original sample with the inclusion of 501 participants (224 males and 277 females). Subsequent data collection at waves two and three also saw a drop in retention rates resulting in further reductions in sample size: 448 participants at 14 years of age (198 males and 250 females) at wave two (88.89% of the original sample), and 410 at 16 years of age (169 males and 241 females) at Wave 3 (81.35% of the original sample).

However, following quality control and population stratification, only white European participants were included in any analysis involving genetic data leaving a reduced sample of 391 (77.58% of the original sample). Of this sample, all 391 participants (191 males and 200 females) with an approximate age of 11-12 years were included at Wave 1. Wave 2 retained 349 participants (167 males and 182 females), that were approximately 14-year of age (69.25% of the original sample), with 40 individuals from Wave 1 either declining to take part at the second wave or excluded due to missing cognitive bias data. Wave 3 retained 323 participants (146 males and 177 females) at approximately 16-year of age (64.09% of the original sample), with a further 33 individuals from the Wave 2 declining to continue at Wave 3 or as in wave 2 excluded due to missing data.

Participants were recruited through their schools by members of the CogBIAS-L-S study team at the University of Oxford. Emails were sent to head teachers or psychology teachers describing the aims of the study, the commitment needed from the school, with offers to work closely with the school on extracurricular projects, such as giving talks to pupils and organising work experience opportunities in the Oxford research lab. Of all the schools invited to participate in the study, only 20% (10 cohorts across nine schools) agreed to take part. Therefore, the CogBIAS-L-S sample was limited to the number of schools willing to participate, as well as parent and child informed consent/assent.

Inclusion criteria for Wave 1, and subsequent waves of the current study were 1) having a parent and adolescent able to give written informed consent/assent, 2) being 12 years old, 3) being able to speak English fluently, and 4) attending a secondary school in England. Potential

participants were excluded if, 1) they were currently suffering with a psychological disorder, or 2) harboured any neurological impairment or learning disability that would make them unable to take part. The latter was indicated by parent self-report.

2.2.3. Procedure

The majority of assessments took place at participant's schools, however, in some cases it was necessary for the assessments to be conducted at the Department of Experimental Psychology, University of Oxford. Assessments across all three waves consisted of two sessions lasting one hour each, and either completed back-to-back, or on different days, depending on the availability of testing space. Participants completed test sessions in small groups within computer labs and were asked to do so under exam conditions. This involved all participants being silent throughout the tasks and attending only to their own computer screen. Participants were asked to give written assent following debriefing whereby the study procedure was explained to them. Across two sessions they completed a batch of cognitive tasks, with the Child Adolescent Survey of Experiences – Child version (CASE–C) questionnaire administered at the end of session one, and the Revised Children's Anxiety and Depression Scale - Short Form (RCADS-SF) at the end of session two. Saliva samples for genotyping were collected during the first wave of data collection at the end of test session two. The Wave 1 testing procedure relevant to the current thesis are given below in **Table 2.2**. For a full breakdown of procedure protocols across the CogBIAS-L-S project please see *"The CogBIAS longitudinal study protocol. Cognitive and genetic factors influencing psychological functioning in adolescence"* (Booth et al., 2017).

Table 2.2. Testing procedure for CogBIAS longitudinal study (Wave 1)

Session One	**Session Two**
Cognitive tasks: Dot-probe task (Attention bias) Adolescent Interpretation and Belief questionnaire (Interpretation bias) *Questionnaire:* The Revised Children's Anxiety and Depression Scale - Short Form (Anxiety and depression) The Child Adolescent Survey of Experiences – Child version (Life experiences)	*Cognitive tasks:* Self-Referential Encoding task (Memory bias) + Saliva samples

2.2.4. Measures

2.2.4.1. Attention bias

A pictorial *dot-probe task* (MacLeod et al., 1986) consisting of both happy and angry faces was used to measure attention bias to two separate emotional categories. An increased attention toward angry vs neutral faces indicated a threat, or negative bias, whilst increased attention toward happy vs neutral faces indicated a positive bias. The task was comprised of two blocks each corresponding to one of the two categories. A total of 56 trials were presented within each of the emotional blocks, featuring an emotional face paired with a matched neutral face (same actor) for 500ms. This was followed by a probe for 3,000ms behind either the emotional (congruent trials) or neutral (incongruent trials) face. Attention bias towards emotion was inferred if the reaction time was faster for congruent trials when compared to incongruent trials. The faces used for the task were selected from the STOIC faces database (Roy et al., 2007), a validated set of six basic emotions expressed by 10 actors. Seven actors (four males, three females) representing three emotions (neutral, anger, happiness) were chosen to make up the task of 112 trials, with each actor being shown 8 times within each block. All faces were presented in greyscale on a grey background with no hair or jawlines visible. All pictures were presented at approximately 10 degrees visual angle apart and were 230x230 pixels in size. To encourage attentional engagement and increase the difficulty of the task probes, corresponding to the correct response, were the letters 'Z' and 'M' and presented equally on the left or right. Following an inter-trial interval (ITI) of 500ms, a fixation cross was presented for 500ms to indicate the start of a new trial. All participants were instructed to focus their attention on the fixation cross, not attend to the faces, and respond to the probe as fast and as accurately as possible. Following an incorrect response, or if no response was given within 3,000ms, an error message was presented. The order of the blocks presented were counterbalanced across all participants, and a rest period of 30,000ms was provided, indicated by a timer that was displayed between blocks. Prior to the actual task all participants completed a practice block which was not included in downstream analysis. These consisted of eight trials depicting only the probe and 16 trials displaying neutral-neutral paired faces. Bias indices were calculated as the difference in reaction time between congruent and incongruent trials (high numbers reflecting attentional orienting). These calculations were performed separately for threat (*angry bias*) and positivity (*happy bias*). Incorrect trials, and those responded to <200ms, >3,000ms or if responses were three standard deviations from each participant's mean reaction time for

each trial type and emotion category were excluded from analysis. Participants with >30% errors overall were also excluded from analysis.

2.2.4.2. Interpretation bias

The Adolescent Interpretation and Belief Questionnaire (AIBQ: (Miers, Blöte, Bögels, & Westenberg, 2008)) was used to measure participants' interpretation bias to hypothetical positive and negative social and non-social scenarios. Participants were presented with 10 ambiguous scenarios (five social and five non-social in nature) and asked to imagine themselves within these scenarios. For example, "You've invited a group of classmates to your birthday party, but a few have not yet said if they are coming". Following this, participants were presented with three interpretive thoughts that may arise as a result of the scenario. Each thought corresponded to either a negative ("They don't want to come because they don't like me"), positive ("They're definitely coming; they don't need to tell me that"), or neutral ("They don't know if they can come or not") interpretation of the scenario. Participants were then instructed to indicate to what extent each of the thoughts would pop into mind using a 5-point Likert scale (1 = does not pop in my mind, 3 = might pop in my mind, 5 = definitely pops in my mind). Outcome variables were then calculated for *positive social interpretation bias* by summing the ratings given regarding the positive social interpretations divided by five (the number of social scenarios), for *negative social interpretation bias* by summing the ratings given regarding the negative social interpretations divided by five (the number of social scenarios), for *positive non-social interpretation bias* by summing the ratings given regarding the positive non-social interpretations divided by five (the number of non-social scenarios), and for *negative non-social interpretation bias* by summing the ratings given regarding the negative non-social interpretations divided by five (the number of non-social scenarios). Scores ranged from 1 to 5. These average scores were then used to create a *social interpretation bias* score (Negative Social – Positive Social) and a *non-social interpretation bias* score (Negative Non-Social – Positive Non-Social), whereby a higher score reflected a greater negative interpretation bias for either social or non-social scenarios respectively. Internal consistency varied for each subscale – *Positive Social Interpretation* (Cronbach's $\alpha = .55$), *Negative Social Interpretation* (Cronbach's $\alpha = .78$), *Positive Non-social Interpretation* (Cronbach's $\alpha = .43$), *Negative Non-social Interpretation* (Cronbach's $\alpha = .56$). As will be discussed in greater detail in chapter 4, adolescence represents a period whereby individuals tend to be more susceptible to social influences (Blakemore, 2018), particularly from their peers (Knoll, Magis-Weinberg,

Speekenbrink, & Blakemore, 2015). Therefore, as the age of the CogBIAS-L-S sample reflects this developmental period, the interpretations of social and non-social events were assessed separately.

Analysis was conducted on overall *social interpretation bias* and *non-social interpretation bias* scores, as well as separately across the positive and negative components (*positive* and *negative social interpretation bias* and *positive* and *negative non-social interpretation bias*).

2.2.4.3. Memory bias

The Self-Referential Encoding Task (SRET: (C. Hammen & Zupan, 1984)) was used to measure memory bias for self-referential words. The task is comprised of three phases which include an encoding phase, a distraction phase, and an incidental free recall phase. In phase one (the encoding phase), self-referential adjectives are displayed on a computer screen for 200ms. Following this, the caption "Describes me?" is then displayed below the word allowing the participant to then respond with either a yes or a no by using the 'Y' or 'N' keys on the computer. Once a valid response has been made a new word is then presented. A total of 22 positive (e.g., "cheerful", "attractive", "funny") and 22 negative (e.g., "scared", "unhappy", "boring") self-referent adjectives were presented throughout the task, each having been validated for use in adolescent samples and matched according to word length and recognisability (C. Hammen & Zupan, 1984). In phase two (the distraction phase) three simple mathematical equations were presented with participants instructed to type their response in the short answer box provided. These responses are not required to be correct and were not included in any downstream analysis. In phase three (the incidental free recall phase) participants were instructed to recall as many words as they could from phase one (the encoding phase), regardless of whether they endorsed the word or not when presented with the caption "Describes me?". Participants were given three minutes to recall as many words as possible before the task ended. *Positive memory bias* was calculated as the total number of positive words that were both endorsed and recalled, and *negative memory bias* as the total number of negative words both endorsed and recalled (Asarnow et al., 2014). An overall *memory bias* score was then computed as: (Negative endorsed and recall – Positive endorsed and recall) / Total. This created a score whereby 0 indicated no memory bias, negative scores indicated more of a positive bias, and positive scores indicated more of a negative bias. Analysis assessed

both the overall *memory bias* score, as well as both the positive and negative components (*positive memory bias* and *negative memory bias*) separately.

2.2.4.4. Life experiences

The Child Adolescent Survey of Experiences – Child version (CASE-C: (J. Allen & Rapee, 2012)) was used to measure both positive and negative life events. This self-report questionnaire is comprised of 38 life events and covers a broad range of both stressful (e.g. "My parents split up") and enjoyable ("I went on a special holiday") experiences. Participants are able to indicate, firstly whether each event had occurred in the previous 12 months, and secondly whether the reported events were positive or negative on a 6-point Likert scale (1 = really bad, 2 = quite bad, 3 = a little bad, 4 = a little good, 5 = quite good, 6 = really good). The number of positive life events and negative life events were then calculated by summing the relevant life events, based on the evaluations given by the participants regarding whether each event was experienced as good or bad, as indicated on the 6-point Likert scale. Following this, the impact of the life events were calculated by assigning 3 points if it was responded to as "really good" or "really bad", 2 points if it was responded to as "quite bad" and "quite good", and 1 point if it was responded to as "a little bad" and "a little good". The summed total of these points was then used to create a Negative Impact Score and a Positive impact score. A higher score indicated a greater positive or negative impact of a given life event. In addition, participants could also report up to two extra significant life events that may have happened to them in the past 12 months. If given, these were then incorporated into the total score. The CASE questionnaire has been shown to have good psychometric properties, with previous research demonstrating that it can distinguish between anxious children and healthy controls (J. L. Allen & Rapee, 2009), as well as identify significant associations between negative life events and depression in adolescent females (Kercher, Rapee, & Schniering, 2009).

2.2.4.5. Depression and anxiety

For the purpose of covarying for current depression and anxiety symptoms, the Revised Children's Anxiety and Depression Scale - Short Form (RCADS-SF: (Ebesutani et al., 2012)), was used. This self-report questionnaire consists of 25-item used to assess anxiety and depression symptoms. The RCADS-SF is comprised of six subscales which correspond to five anxiety subscales including separation anxiety, generalized anxiety, panic disorder, social anxiety, obsessive compulsive disorder and a single depression scale. All items are ranked on

a 4-point Likert scale (Never=0 to Always=3). All items relating to anxiety, including those corresponding to each of the anxiety subscales (separation anxiety, generalized anxiety, panic disorder, social anxiety, and obsessive-compulsive disorder) are summed to create a total anxiety score. Similarly, all items relating to depression are also summed to create a depression total score. In both cases, a higher score represents increased symptoms of either depression or anxiety in adolescents. The RCADS-SF is a derivative of the original 47-item questionnaire (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000), and has been demonstrated as having good reliability and validity across both children and adolescents (Chorpita, Moffitt, & Gray, 2005).

2.2.5. Genotyping

Saliva samples were collected from 499 (99%) of the original 504 participants at Wave 1 using *DNA Genotek Oragene OG-500* collection kits in accordance with the supplied instructions. Genomic DNA was extracted using an established protocol and stored at -80°C. In total 496 participants provided an adequate yield of DNA (200ng) and were genotyped, per manufactures instructions, using the Illumina Human Omni express-24 chip, which captures 710,000 single nucleotide polymorphisms (SNPs) from across the genome. This chip assays most genetic variants implicated in sensitivity to the environment, either directly or through imputation. It is therefore considerably more cost effective and requires less DNA per variant than candidate-gene genotyping. Genome-wide data was subject to rigorous quality control using an established pipeline resulting in 594,667 SNPs across 491 participants remaining for downstream analysis with an additional 5,129,755 SNPs imputed using the 1000 Genomes reference panel.

In addition to genome-wide genotyping and imputation, and specific to study two (Chapter four), 496 of those participants that provided saliva samples (99.4% of the initial 499) were also separately genotyped for the serotonin transporter polymorphism (5-HTTLPR) using an established polymerase chain reaction (PCR) protocol. 4ul of DNA from each sample and 16ul of mastermix were loaded across 14 96-well plates. The PCR mastermix per sample consisted of 2ul of NH4 buffer, 1.2ul of magnesium ($MgCI^2$), 0.5ul of dNTPs, 0.4ul of forward primer (5'-TCCTCCGCTTTGGCGCCTCTTCC-3'), 0.4ul of reverse primer (5'-TGGGGGTTGCAGGGGAGATCCTG-3'), 0.2ul of hot star Taq, and 11.3ul of sterilised H^2O. Due to the nature of hot star Taq it was necessary to make up and load the mastermix on ice, and as quickly as possible. The thermocycling conditions for the PCR reaction consisted of

three stages as follows: Stage 1: 95°C for 15 minutes, Stage 2: 34 cycles at 94°C for 30 seconds, 63.4°C for 1 minute 30 seconds and 72°C for 1 minute, Stage 3: 72°C for 10 minutes. Upon completion of the PCR reaction, the resulting PCR product was then run on a 2% agarose gel for 1 hour and 35 minutes. An example of a successful PCR reaction can be seen in **Figure 2.1**.

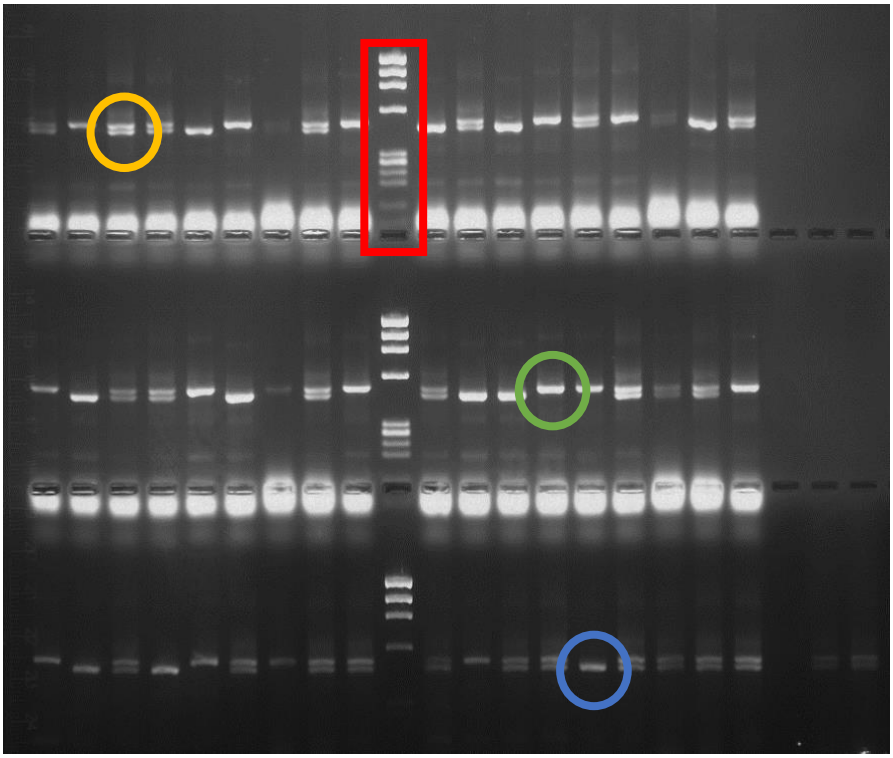


Figure 2.1. Image of a successful PCR run on 2% agarose gel.

In **Figure 2.1**, the two horizontal bands circled in yellow represent an individual with a heterozygote LS genotype. The single band circled in green shows an individual with a homozygote LL genotype, whilst the band circled in blue, which is slightly lower against the genomic ladder (red rectangle), compared to the band circled in green, signifies a homozygote SS genotype. The bands in the red rectangle provide a reference for the length/size of a DNA molecule in the form of a 1 kilobases (kb) genomic ladder.

Providing the PCR had been successful, and callable signals had been obtained regarding the samples allele combination, the remaining PCR product was then used for the restriction enzyme digest to obtain the 5-HTTLPR single nucleotide polymorphism (SNP) data regarding rs25531. Firstly, an aliquot of 6ul of PCR product was combined with 4ul of mastermix in a PCR plates with the same sample layout to avoid mismatching of sample IDs. The mastermix for the enzyme digest consisted of 1ul Cutsmart buffer, 0.25ul of HpaII, 0.1ul

of 100xBSA and 2.64ul of sterilised H^2O. The incubation condition for the enzyme digest was set at 37°C and lasted for 16 hours. Similar to the PCR reaction, upon completion the enzyme digest product was then run on a 3% agarose gel for between 1.5/2.5 hours, until the bands had separated sufficiently to call. An example of a successful enzyme digest reaction can be found in **Figure 2.2**.

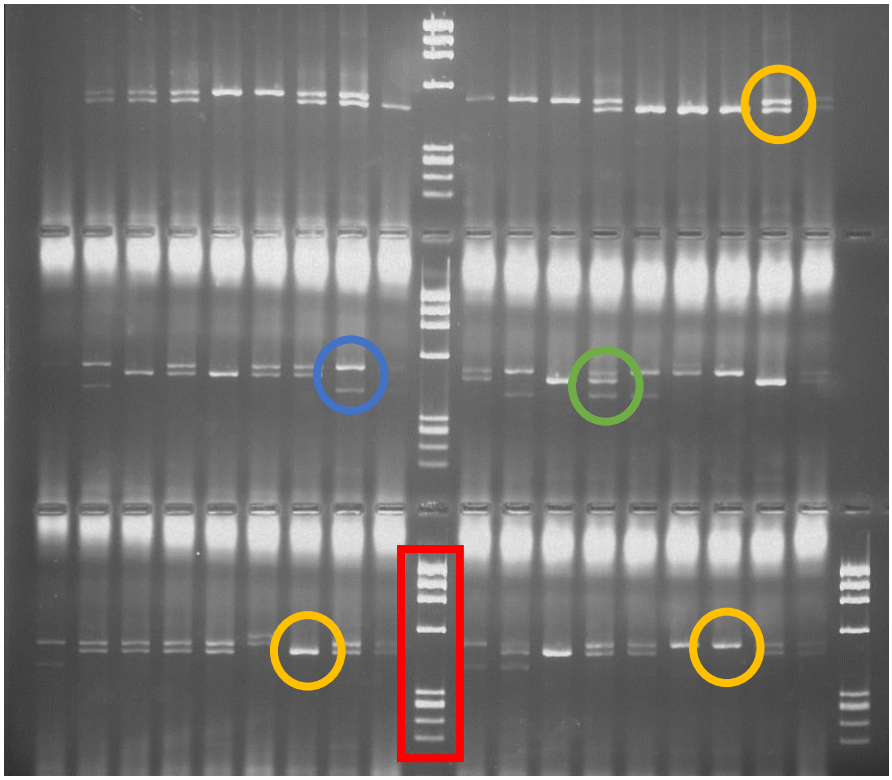


Figure 2.2. Image of a successful enzyme digest reactions run on 3% agarose gel.

In **Figure 2.2**, the bands circled in blue show an individual with a homozygote La/Lg genotype, with 'g' signifying the presence of an LPR SNP on a long allele. The bands circled in green represent those with a heterozygote La/Sg genotype, with 'g' signifying the presence of an LPR SNP on a short allele. Those bands circled in yellow represent the three genotypes described in the previous figure that are without the LPR SNP. The bands in the red rectangle as mentioned above is a 1 kilobases (kb) genomic ladder that gives an approximate indication of the length/size of the DNA molecule.

2.2.6. Candidate gene selection

All selected genetic variance had been previously implicated to increase sensitivity to environmental effect in GxE studies of symptoms and traits related to depression and anxiety,

or depression and anxiety directly. A systematic Pubmed search was conducted using the terms “gene environment interaction” against the search terms “environmental sensitivity”, “candidate gene studies”, “psychopathology”, “depression”, “anxiety”, “cognitive bias”, “stressful life events”, “childhood maltreatment”, “emotional reactivity”, “differential susceptibility”, and “psychological treatment response” in all fields. The systematic search identified 28 candidate genes across 15 studies (see **Table 2.3**).

Table 2.3. The list of candidate genes and variants included in the study based on the systematic PubMed search.

Gene	Variant	Sensitivity Allele	Previous Research	GxE findings	In CSS
FAAH	rs324420	A	(Lazary, Eszlari, Juhasz, & Bagdy, 2016)	Moderated chronic childhood adversity on depression and anxiety	YES
NGF	rs6330	T	(Hudson et al., 2013)	Moderated response to psychological treatments for Anxiety	YES
OXTR	rs53576	C	(Chang et al., 2014)	Moderated Oxytocin/dopamine interaction and neuroticism traits	YES
GSK3B	rs6782799	C	(Bousman, Gunn, Potiriadis, & Everall, 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
NR3C2	rs5522	Val (G)	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
HTR1A	rs878567	C	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
FKBP5	rs3800373	G	(Scheuer et al., 2016)	Moderated adverse life events on depression and anxiety risk	YES
FKBP5	rs1360780	T	(Scheuer et al., 2016)	Moderated adverse life events on depression and anxiety risk	NO
FKBP5	rs4713916	A	(Scheuer et al., 2016)	Moderated adverse life events on depression and anxiety risk	NO
CNR1	rs7766029	T	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
CNR1	rs1049353	G	(Agrawal et al., 2012)	Moderated childhood physical abuse on anhedonic depression	NO
OPRM1	rs1799971	A	(Slavich, Tartter, Brennan, & Hammen, 2014)	Moderated socially unpleasant life events on depression	YES
NPSR1	rs324981	T	(Klauke et al., 2014)	Moderated life events on anxiety sensitivity	YES
BDNF	rs6265	Met (T)	(van Winkel et al., 2014)	Moderated social stress on depression symptoms	YES
DRD2	rs1800497	T	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
HTR3A	rs1062613	T	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
TPH1	rs1800532	T	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
TPH2	rs4570625	T	(Forssman et al., 2014)	Moderated early life stress on heightened attention to social fear	YES
HTR2A	rs6314	A	-	-	NO
HTR2A	rs6313	T	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
HTR2A	rs6311	A	-	-	NO
SLC6A2	rs2242446	C	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
SLC6A2	rs5569	A	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
SLC6A4	5HTTLPR	S	(Caspi et al., 2003)	Moderated life events and childhood maltreatment on depression	YES
SLC6A4	rs25531	G	-	-	YES
CRHR1	rs110402	A	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
CHRNA4	rs1044396	T	(Grazioplene, DeYoung, Rogosch, & Cicchetti, 2013)	Moderated childhood maltreatment on personality/developmental sensitivity	YES
COMT	rs4680	Val (G)	(Baumann et al., 2013)	Moderated early life experiences on Anxiety sensitivity	YES

Note: Two variants (rs6314 and rs6311) were also included due to being in high linkage disequilibrium (LD) with rs6313 which was selected as a result of the systematic PubMed search. The last column of the table also indicates whether a variant was included in the candidate sensitivity score. Variants in LD with other variants in the same gene were randomly removed from the candidate sensitivity score to prevent type I error.

2.3. Study Three (Cognitive biases as potential mechanisms mediating genetic risk for depression and anxiety: A phenome-wide approach)

2.3.1. Design

Like study two (Chapter 4), study three (Chapter 5) was also designed based on the CogBIAS-L-S to assess specific aspects of the CogBIAS hypothesis. For further details regarding the design of the CogBIAS-L-S please see Chapter 2 (**Section 2.2.1).**

In more detail, study three (Chapter 5) was designed specifically to assess whether cognitive biases in memory and interpretation share genetic architecture with major depression and whether such cognitive biases, present in adolescents, might mediate genome-wide genetic risk for depression on the later emergence of depression and anxiety symptoms. A phenome-wide polygenic approach was taken to assess whole-genome data and measures of depression, anxiety and cognitive biases, across three waves of the CogBIAS-L-S, and their associations with an adult polygenic risk score (PRS) for major depression. Associations between the MDD PRS and the phenome-wide data regarding the cognitive biases, depression and anxiety scores were assessed both within and across all waves and at multiple p-value thresholds. The percentage of variance explained across all cognitive and affective phenotypes by the adult PRS were also assessed. Mediation analysis was then conducted with further examination of the most significant findings to assess the robustness of the mediation and any potential causal relationships.

2.3.2. Sample

Study three (Chapter 5) utilised the same CogBIAS-L-S sample used in study two (Chapter 4). However, as study three was concerned purely with genetic associations and mediation of genetic risk for depression and anxiety by cognitive biases only the subsample of Europeans (n = 391) were used across the current study. See the Chapter 2 (**Section 2.2.2**) for further details regarding this sample.

2.3.3. Measures

2.3.3.1. Memory bias

As with study two (Chapter 4), Memory bias was assessed using The Self-Referential Encoding Task (SRET: (C. Hammen & Zupan, 1984)). This memory bias measure consisted

of positive and negative scores that were used to calculate an overall *memory bias* score. Both the overall *memory bias* scores and the corresponding positive and negative components (*positive memory bias* and *negative memory bias*) were assessed separately throughout Chapter five. See Chapter 2 (**Section 2.2.4**) for detailed information regarding this memory bias measure.

2.3.3.2. Interpretation bias

In keeping with study two (Chapter 4), interpretation bias was assessed using The Adolescent Interpretation and Belief Questionnaire (AIBQ: (Miers et al., 2008)). This interpretation bias measure consisted of positive and negative scores for the interpretation of social scenarios (*positive social interpretation bias* and *negative social interpretation bias*) and positive and negative scores for the interpretation of non-social scenarios (*positive non-social interpretation bias* and *negative non-social interpretation bias*). These scores were used to calculate two overall bias scores for *social interpretation bias* and *non-social interpretation bias*. As with memory bias, analysis throughout Chapter five assessed both the overall *social* and *non-social interpretation bias* scores as well as the four corresponding positive and negative components (*positive* and *negative social interpretation bias* and *positive* and *negative non-social interpretation bias*) separately. See Chapter 2 (**Section 2.2.4**) for detailed information regarding this interpretation bias measure.

2.3.3.3. Depression and Anxiety

The Revised Children's Anxiety and Depression Scale - Short Form (RCADS-SF) (Ebesutani et al., 2012), also used in study two (Chapter 4), was used to assess depression and anxiety symptoms. See the study two measures section in the current methods (Chapter 2) for detailed information regarding this depression and anxiety measure.

2.3.3.4. Major depressive disorder (MDD) polygenic risk score (PRS)

Specific to study three (Chapter 5) was the use of a publicly available MDD PRS obtained from the psychiatric genomic consortium (see http://pgc.unc.edu). The MDD PRS was originally created from the summary statistics of a large scale genome-wide association study meta-analysis of depression (N. R. Wray et al., 2018). These summary statistics, consisted of data from the core 29 PGC MDD2 cohorts, with the addition of the deCODE, Generation Scotland, Genetic Epidemiology Research on Adult Health and Aging (GERA),

and iPSYCH cohorts. The UK Biobank and 23andMe cohorts were excluded and any overlap from other cohorts with the UK Biobank were removed as these datasets are not publicly available. The MDD PRS included a total of 9,884,712 variants from 45,396 cases and 97,250 controls.

These 9,884,712 variants were used as the basis to create PRS for each individual within the CogBIAS sample at different *p*-value thresholds. Each threshold included a different number of variants from the original MDD PRS that were also present in the CogBIAS-L-S sample. These were then regressed against scores regarding each phenotype. The number of variants at each threshold ranged from 8,173 variants at the *p*-value threshold 0.01, to 114,860 variants at the *p*-value threshold 1 (all available variants).

The MDD PRS was used throughout study three (Chapter 5) to assess multiple associations and variance explained for all cognitive biases and their positive and negative components, as well as measures of depression and anxiety across the CogBIAS-L-S sample at multiple *p*-value thresholds. The same MDD PRS scores, at specific thresholds, was also used as the independent variable for all mediation models assessing the mediation of genetic risk for depression by all cognitive biases and their positive and negative components (mediator variables) on later depression and anxiety symptoms (dependant variables).

2.3.4. Genotyping

Saliva samples were collected using *DNA Genotek Oragene OG-500,* and genotyping was conducted using the Illumina Human Omni express-24 chip capable of capturing up to 710,000 genome-wide SNPs. Further information regarding the genotyping, quality control and imputation of the CogBIAS-L-S sample is provided in detail in Chapter 2 (**Section 2.2.5**).

2.4. Approaches to analysis across all empirical chapters

Linear mixed models (LMM) were used throughout the current thesis to investigate the effects of cognitive biases, genes, environments and gene-by-environment interactions (unless otherwise stated). Outcomes varied depending on the study chapter and what aspect of the CogBIAS hypothesis was under investigation.

Modelling the associations between repeat measures within the same individual as random effects allowed for the use of all available collected data from each wave, whilst also accounting for the non-independence of data collected longitudinally. Unlike more traditional

end-point analyses, this approach is not conditional on the retention of the whole sample across all three waves of data collection to assess outcomes. Furthermore, it does not depend on imputation methods which have been shown to introduce potential biases such as last observation carried forward (LOCF) (Gueorguieva & Krystal, 2004). Another benefit of LMM is the inclusion of higher order random effects. As analysis for study two (Chapter 4) highlighted a moderate effect of wave on cognitive biases wave was modelled as a higher-order random effect in all analysis concerning the CogBIAS-L-S sample. This was also the case for the random effects of time in the separate sample used in study one (Chapter 3).

Other than random effects, LMM can also include fixed effects. This section of the models included both the predictors under investigation (e.g., genotypes, life events, or cognitive biases) as well as covariates. All models across all study chapters included the linear effects of time as covariates (thus all models considered the fixed and random effects of time), as well as both age and sex. Where specified, environmental factors and depression and anxiety scores were also used as covariates.

In keeping with standard linear regression, the fixed effects of components within the models were expressed as beta coefficients alongside confidence intervals and p-values indicating significance. Statistical analyses were conducted in STATA version 12.1 (StataCorp, 2011). Further details regarding specific analyses are provided in each of the study chapters.

Lastly, both nominally significant findings as well as those that are significant following correction for multiple testing (False Discovery Rate: FDR) will be interpreted throughout the current thesis, particularly in study two (Chapter 4) and study three (Chapter 5). This is due to the exploratory nature of the research, as this is the first time that such associations have been assessed, and also as the CogBIAS-L-S sample is relatively small in comparison to other samples used in genetic association studies. It is believed that nominal associations, whilst potentially spurious and a result of type I error, may also reflect a lack of statistical power and therefore worth identifying as potential targets for further study.

3. Chapter 3 - Cognition and Response to Environmental Stimuli (CRESt): The effect of cognitive biases on affective states in response to daily life events

3.1. Introduction

As highlighted throughout Chapter one there has been a considerable amount of research attention regarding environmental sensitivity, emotional reactivity and psychiatric disorders such as depression and anxiety. While cognitive biases have also been assessed in relation to the onset and maintenance of depression and anxiety using experimental designs, these lines of research have often remained separate. Furthermore, despite the link between environmental sensitivity and mood disorders having been proposed, the role of emotional reactivity and cognitive biases have been somewhat overlooked in terms of potential mechanisms regarding these relationships. Therefore, in order to investigate the possible role played by cognitive biases in the development of depression and anxiety the logical first step is to assess whether biases in attention, interpretation and memory impact on an individual's response to everyday activities and environments. This chapter therefore aims to examine:

1) The effect of cognitive biases on the *level* of positive and negative affect throughout the course of daily life,
2) The effect of cognitive biases on the *variability* of positive and negative affect throughout the course of daily life,
3) The impact of cognitive biases on the perceived quality of day-to-day contextual events, and,
4) The extent to which cognitive biases moderate the effects of positively and negatively perceived events on levels of positive and negative affect.

3.1.1. The effect of cognitive biases on emotional reactivity and mood

Although research has demonstrated that elevated emotional reactions to stressful events reflects increased susceptibility to anxiety and depression, the mechanisms that underlie these processes are still somewhat unknown. Whilst there has been considerable research examining the relationship between cognitive processes and emotional regulation in psychiatric disorders such as depression (for a comprehensive review see: (Joormann & Quinn, 2014)), there have been few studies to date that have assessed the effect of cognitive biases on emotional reactivity to stress in otherwise healthy samples (Fox et al., 2010). This is of

particular importance as existing psychopathology makes it very difficult to infer any causal relationship.

Fox et al (2010) was the first prospective study to examine the association between cognitive biases and emotional reactivity in healthy individuals. Specifically, they assessed a sample of 104 male psychology students at baseline for both preconscious and conscious attention bias towards negative or positive images using a dot-probe task. The task itself consisted of an equal number of aware (conscious) and unaware (preconscious) trials whereby the stimulus presented was masked with fragments of other images after 14ms (preconscious subliminal measure of attention bias) or 300ms (conscious measure of attention bias). Depression symptoms were also assessed using the Beck Depression Inventory (BDI), as were the 'the Big Five' personality traits using a short-form of the NEO Personality Inventory (Costa & McCrae, 1985). Following an initial baseline measures, 82 returning participants were then retested four months later, with a final testing phase of 70 of the initial 104 another four months later. At the first retest phase of four months the returning participants were required to prepare and give a five-minute presentation in front of a camera and two examiners as way of inducing experimental stress. Measures of state anxiety were taken 20-minute prior and five minutes after the presentation. At the final eight-month testing phase the same measures were taken before and after a naturalistic stress task represented by their end of year exams. Interestingly, findings demonstrated that selective preconscious attentional processing of negative material represented a more reliable predictor of later emotional reactivity than measures obtained through self-report regarding levels of neuroticism, anxiety or extraversion.

Other studies have been conducted examining the effects of cognitive biases on mood reactivity and recovery (Clasen et al., 2013), and on emotional reactivity (LeMoult et al., 2013), however these have all been cross-sectional in nature. Despite this, these studies have demonstrated associations between cognitive biases and emotional/mood reactivity. For example, Clasen et al (2013), assessed 48 individuals with, and 224 without MDD for attention bias using a modified exogenous cuing task which utilised emotional facial expression (Posner, 1980). In addition to attention bias, a measure of sad mood was obtained using Profile of Mood States (POMS: (McNair, Lorr, & Droppleman, 1992)). This was assessed before, immediately after and a further twenty minutes after participants had received one of two mood induction tasks to which they had been randomly assigned. In those without depressive symptoms they demonstrated that whilst there was a strong association between mood reactivity and recovery, with reactivity successfully predicting recovery, the association was significantly moderated

by an attention bias towards negative facial expressions. This could potentially imply that attention bias towards negative stimuli is a causal mechanism by which the rate of recovery is reduced following a negatively induced mood. Indeed, there have been several studies examining multiple cognitive biases, demonstrating that experimentally induced or modified biases can impact on subsequent emotional reactivity (E. Watkins, Moberly, & Moulds, 2008) and mood (Lothmann, Holmes, Chan, & Lau, 2011) further suggesting a potential causal associations.

These studies demonstrate the association between cognitive biases and personality traits, as well as mood and emotional reactivity, whilst also drawing attention to the need for more research in this specific area. However, other than Fox et al. (2010) there has been little research investigating these effects in longitudinal settings, and few studies (cross-sectional or otherwise) tend to assess more than a single bias (typically attention bias). Furthermore, research assessing the effects of cognitive biases on mood, such as that described above, tends to rely on using anxiety state as a measure of negative mood, often with no measure of positive mood state.

Positive and negative affect (PA and NA respectively), both classically measured by the Positive and Negative Affect Schedule (PANAS), represent separate yet associated collections of affective states and are by themselves unique dimensions that tend to be negatively correlated within individuals (Crawford & Henry, 2004). PA, a reward focused dimension, represents affective states that include being cheerful, enthusiastic, and content. In contrast, NA, a threat focused dimension, encapsulates affective states such as loneliness, guilt, and stress. Furthermore, whilst PA is related to behavioural approach/engagement with environmental situations, NA is related to avoidance or withdrawal from environmental situations (Clark, Watson, & Mineka, 1994; Watson, Wiese, Vaidya, & Tellegen, 1999). PA and NA reactions can therefore be seen as preparation for an individual to adapt to opportunities and threats within the environment (Watson et al., 1999).

Like cognitive biases, traits associated with PA such as optimism, humour, as well as the ability to experience reward and pleasure have also consistently been said to predict stress response (Bonanno, 2004; Charney, 2004; Folkman & Moskowitz, 2000; Fredrickson, 2001; Haglund, Nestadt, Cooper, Southwick, & Charney, 2007; Southwick, Vythilingam, & Charney, 2005; Tugade, Fredrickson, & Feldman Barrett, 2004). With this in mind, assessing the effect of cognitive biases on levels of affect in response to positive (rewarding) and negative

(stressful) events would likely reveal important information regarding the relationship between stress and cognitive biases on levels of affect.

However, once again the issue remains that most, if not all of these studies have been conducted in experimental settings, with the use of self-report retrospective questionnaires for the majority of measures. The inclusion of methods such as experience sampling (ESM), to assess such effects would allow for more ecologically valid assessments in day-to-day environments with measures taken in the moment, rather than retrospectively. Furthermore, this approach is also perfectly suited for more in-depth longitudinal assessments of these effects over time, likely providing researchers with much more detailed and accurate information regarding these effects in everyday life.

3.1.2. The effects of daily life events on affect: Experience sampling approaches

The use of an ESM approach for data collection allows for both within-subject assessments over time and between-subject comparisons. It is also seen as more ecologically valid than other approaches as it occurs in the participants' natural day-to-day environment. Furthermore, ESM research is a method that has proven to be very popular and capable at examining the finer aspect of mood states, including both PA and NA (Hundt et al., 2013; Komulainen et al., 2014; Wichers et al., 2007).

In a study by Komulainen et al. (2014) examining the effect of personality on day-to-day levels of affect, data was collected from 104 healthy students at 10 timepoints throughout a normal day for one week using an experience sampling method. Participants reported their repeated measures of daily life affect by responding to questions such as "Right now I feel sad" on a 7-point Likert scale. Participants were also prompted to report activities at the time of a notification, events prior to the notification, whether they were socially engaged, and their own subjective evaluation of these events. This information collectively formed measures regarding the perceived quality of daily life contexts, with levels of affect in response to each of these daily life contextual variables used to measure affect reactivity. Before the experience sampling began each participant was assessed for personality traits using the NEO Five Factor Inventory (NEO-FFI). As expected, higher neuroticism was associated with greater NA and lower PA, greater variability in levels of affect and reactivity to stress, and more negative ratings of events. Conversely, conscientiousness was found to significantly predict lower average levels of both reactivity to daily stress and NA. Agreeableness, extraversion and openness were also found to have significant associations across the emotional processes examined. These results

demonstrate that individual differences in personality traits, particularly neuroticism, have a significant impact on levels of PA and NA as well as reactivity to daily life stressors.

Another earlier ESM study also assessed the association between sensitivity to punishment and reward, and levels of affect as well as how individuals perceived their daily life situations (Hundt et al., 2013). Using very similar self-report measures as Komulainen et al. (2014), researchers demonstrated, in a sample of 180 students, that sensitivity to punishment was positively associated with NA and negatively associated with PA in the course of daily life. Conversely, reward sensitivity was positively associated with PA and negatively associated with the irritability/anger aspect of the NA dimension. Additionally, those individuals with higher levels of sensitivity to punishment were also seen to show less increase in PA and decreases in NA in several positively perceived situations when compared to those with lower sensitivity to punishment. Furthermore, those with higher reward sensitivity showed a greater decline in NA across several positively perceived situations when compared to those with lower reward sensitivity. These results provide ecologically valid evidence, and further conformation regarding the association between reward sensitivity and PA and sensitivity to punishment and NA.

Whilst previous research has assessed the effect of traits such as personality and reward/punishment sensitivity on levels of affect in day-to-day life, similar approaches are yet to be applied to examine the impact of cognitive biases on these same affective dimensions. As highlighted earlier, research has demonstrated cognitive biases in attention as a more reliable indicator of later emotional reactivity than either neuroticism or extraversion, whilst also highlighting associations between them (Fox et al., 2010). Therefore, examining the relationship between cognitive biases and PA and NA using ESM will likely demonstrate a similar or greater effect of cognitive biases on levels of affect in day-to-day life.

It seems that what is needed is an ESM approach examining the effect of multiple cognitive biases on both PA and NA in response to daily life contexts in individuals with no current psychopathology. This would echo and extend on the work of Komulainen et al. (2014), with the big five personality traits being replaced with cognitive biases in attention, interpretation and memory, and would likely provide valuable in-depth information regarding the effect of these biases on levels of affect in varying contexts of daily life.

3.1.3. Aims and Hypothesis

The overarching aim of the current study is to investigate the relationship between cognitive biases and response to both positive and negative daily life events using an ESM design. More specifically the current study aims to assess the effects of cognitive biases on PA and NA in daily life over a seven-day period. Here, it is expected that there will be associations found between cognitive biases and levels of PA and NA throughout the ESM period.

Secondly, the current study also aims to examine the effects of cognitive biases on the variability of PA and NA. Whilst there is no direct empirical evidence to inform a hypothesis here, the CogBIAS hypothesis and the ESM study by Komulainen et al. (2014) provide some theoretical basis to expect an association between cognitive biases and affect variability.

Thirdly, the current study will assess the effects of cognitive biases on the perceived quality of environmental contexts including, the quality of previous events (prior to ESM notifications), the quality of current activities (both enjoyment and ability), and the quality of present company, which will assess both solitude if alone, or social interaction if not alone at the time of the notification. Here, it is hypothesized that cognitive biases will show associations with how the quality of environmental contexts are perceived.

Lastly, following an assessment regarding the effects of the environmental contexts on levels of PA and NA, which is expected highlight significant associaions, the effects of cognitive biases on affect reactivity in response to positive and negative daily environmental contexts will be investigated. This will be examined by assessing the interactions between each of the cognitive biases and each of the environmental contexts (both positive and negative) on levels of both PA and NA. This is expected to reveal that affect reactivity in response to positive and negative daily environmental contexts is associated with levels of cognitive biases.

3.2. Methods

3.2.1. Design

Following baseline tests of cognitive biases in attention, interpretation and memory, an ESM smart phone application, that was specifically designed for use in the CRESt study, assessed mood states and experiences at repeat intervals throughout the course daily life. Participants received eight notifications per day between 10.30am and 10.30pm for a period of no less than seven days. Further detailed information regarding the study design can be found in Chapter 2 (**Section 2.1.1**).

3.2.2. Sample

A total of 100 participants (17 Male, 83 female) completed the cognitive testing and seven days of experience sampling. However, following quality control of the data a final total of 74 participant (12 Male, 62 female) remained for downstream analysis. Ages of the participants ranged from 18-30 with a mean age of 22.51. Further information regarding the CRESt sample is given in Chapter 2 (**Section 2.1.2**).

3.2.3. Ethics

The study obtained ethical approval from the QMUL ethics committee. All participants verbally consented to take part in the study and were debriefed accordingly following the studies completion. Further details regarding the ethical considerations pertaining to the current study are given in Chapter 2 (**Section 2.1.3**).

3.2.4. Procedure

Participants scheduled a meeting at their convenience to come to QMUL for cognitive bias testing, whereby they were subsequently instructed on how to install and use the ESM application. All participants were given £50 worth of "Love to shop" vouchers as incentive for taking part in the study. More detailed information regarding the study procedure is provided in Chapter 2 (**Section 2.1.4**).

3.2.5. Measures

A modified *Dot-Probe Task* (MacLeod et al., 1986) assessing reaction times to positive and negative images was used to assess attention bias. Interpretation bias was assessed using *The Scrambled Sentence Task* (SST: (Wenzlaff, 1991)), which required participants to address twenty scrambled sentences. Memory bias was assessed using *The Self-Referential Encoding Task* (SRET: (C. Hammen & Zupan, 1984)), which assessed the number of positive and negative words endorsed and recalled by each participant. All cognitive bias measures provided both positive and negative bias scores that were used to calculate an overall bias score. The primary focus of analysis throughout the current study was concerned with the overall bias scores. However, following a significant finding each of the positive and negative bias components were assessed separately. See Chapter 2 (**Section 2.1.5**) for detailed information regarding these measures.

At each notification participants provided contextual information by responding to a series of questions, regarding the most recent previous event, current activity and nature of their company. To assess affective states at the time of the notification participant were required to indicate, on a 7-point Likert scale, to what extent they identified with a phrase which included a word associated to either PA or NA. A more detailed description of both context and affect measure are given in Chapter 2 (**Section 2.1.5.4**).

3.2.6. Statistical analysis

Linear mixed-effect models were used for the analysis regarding the main effects of cognitive biases on daily life level of affect and the effects of cognitive biases on daily life context, with logistic regression models used in the case of binary responses. This statistical approach was used as it takes into account the hierarchical structure of the data and is robust to repeated measures at a within-subject level and any occurrence of unequal number of measures. Analysis of the data was conducted using the STATA 12 statistical software package (StataCorp, 2011). Each of the cognitive biases and their positive and negative components were included in the models as fixed effects. The notification number from the ESM smartphone application (no more than 56 over the seven-day period) operated as the time of notification and was included in the models as both a fixed effect, and random effect, varying at random between participants. So as to allow for the comparison of regression coefficient all variables were standardised accordingly. All models also controlled for the age and sex of the participants.

In the first model, the effect of cognitive biases on daily life level of affect was assessed using PA and NA scores (the collective effect of the respective PA and NA variables) as a dependant variable and each of the cognitive biases as predictors. Bivariate correlation analysis was also conducted to assess affect variability as a result of variations in cognitive biases. Standard deviation for each of the affect variables were calculated across all responses of each participant. Following this, correlations between each standardised cognitive bias score and affect variable standard deviation were calculated.

The second model assessed the effect of cognitive biases on the quality of daily life contextual events. Subjective ratings regarding previous events formed the measure "Quality of previous event", whilst those regarding ability and enjoyment of current activity were summed to form the measure "Quality of current activity". The measures "Quality of solitude" and "Quality of social interaction" were created from binary responses regarding present company. Specifically, being alone by choice, and being alone but not by choice formed the measure "Quality of solitude", while being content with the present company of another and preferring to be alone in comparison formed the measure "Quality of social interaction". The four daily life contextual measures were then used as dependant variables with each cognitive bias used again as predictors. This model was then rerun to assess the effect of the same subjective daily life contextual events on levels of PA and NA. Here levels of PA and NA were used as dependant variables, and subjective daily life contextual events used as predictors.

Lastly, in models three and four, interaction effects between cognitive biases and each daily life contextual measure were examined to assess effects on PA and NA reactivity. These analyses were performed separately for PA and NA outcomes.

3.3. Results

3.3.1. Descriptive analysis

On average participants responded to 51.31 notifications across seven days of experience sampling (SD=2.56, range=41-56). The total number of completed sessions from all notification and across all participants within the final dataset was 2,529. Descriptive statistics regarding the ESM measures of PA and NA, context, and the cognitive biases are provided in **Tables 3.1** and **Table 3.2**.

Table 3.1. Displaying the mean, standard deviation, and minimum and maximum scores for positive and negative affect and context given in response to the repeat measures in the moment experience sampling smart phone application over the course of seven days.

Positive affect:	**Mean**	**Std Dev**	**Min**	**Max**
Cheerful	4.14	1.48	1.00	7.00
Enthusiastic	4.00	1.51	1.00	7.00
Relaxed	4.26	1.49	1.00	7.00
Content	4.28	1.39	1.00	7.00
Safe	5.73	1.36	1.00	7.00
Negative affect:	**Mean**	**Std Dev**	**Min**	**Max**
Worried	2.82	1.57	1.00	7.00
Tense	2.93	1.60	1.00	7.00
Down	2.60	1.54	1.00	7.00
Lonely	2.25	1.46	1.00	7.00
Guilty	2.22	1.54	1.00	7.00
Stressed	3.34	1.67	1.00	7.00
Contexts	**Mean**	**Std Dev**	**Min**	**Max**
Notifications when alone	24.97	14.84	1	55
Previous Event (Pleasant or unpleasant)	4.77	1.50	1.00	7.00
Quality of current activity (Enjoyment)	4.73	1.60	1.00	7.00
Quality of current activity (Ability)	5.07	1.36	1.00	7.00
Present company	1.52	0.50	1.00	2.00
Alone by choice	1.33	0.47	1.00	2.00
Prefer to be alone	1.79	0.40	1.00	2.00

Table 3.2. Displaying the mean, standard deviation, and minimum and maximum scores for cognitive biases in attention, interpretation and memory, and their positive and negative components, prior to the experience sampling.

Cognitive biases	Mean	Std Dev	Min	Max
Attention bias	-3.78	30.73	-151.46	69.45
Positive attention bias	-1.08	25.60	-79.94	45.49
Negative attention bias	1.90	37.67	-98.05	122.13
Memory bias	-0.30	0.35	-1.00	0.67
Positive memory bias	4.68	1.81	1.00	9.00
Negative memory bias	2.69	1.68	0.00	7.00
Interpretation bias	-0.46	0.40	-1.00	0.80
Positive interpretation bias	13.17	3.79	2.00	20.00
Negative interpretation bias	4.89	3.75	0.00	18.00

3.3.2. Reliability analysis – Measures of positive and negative affect

Factors contributing to both PA and NA were assessed in order to examine whether these factors were adequately loading on to the according PA or NA dimensions. To begin with, the correlation between individual variables within the PA and NA dimensions were assessed. The results can be found in the correlation matrix in **Table 3.3**.

As can be seen in **Table 3.3**, the PA variables cheerful, enthusiasm, relaxation and content all had significant positive associations with each other, whilst also having negative associations with the NA variable. However, the variable safety, despite showing negative associations with the NA variables to some extent did not have a significant positive correlation with any of the PA variables.

Results regarding the associations between the individual NA variables highlighted significant correlations between worried, tense, down, loneliness and stress. However, the NA variable guilt, whilst showing a significant association with the variable loneliness, showed no significant positive associations with the remaining four variables worried, tense, down or stress. Furthermore, with the exception of safety, guilt showed no significant negative associations with the individual PA variables and was also positively associated with the PA variable enthusiasm.

Table 3.3. Correlation matrix displaying the associations between the individual positive and negative affect variables.

	Cheerful	Enthusiasm	Relaxation	Content	Safety	Worried	Tense	Down	Loneliness	Guilt	Stress
Cheerful	1	-	-	-	-	-	-	-	-	-	-
Enthusiasm	**.680*** **	1	-	-	-	-	-	-	-	-	-
Relaxation	**.597*** **	**.546*** **	1	-	-	-	-	-	-	-	-
Content	**.609*** **	**.481*** **	**.708*** **	1	-	-	-	-	-	-	-
Safety	.186	.102	.202	.076	1	-	-	-	-	-	-
Worried	**-.316***	-.233	**-.528*** **	**-.574*** **	-.162	1	-	-	-	-	-
Tense	**-.307***	-.239	**-.581*** **	**-.418*** **	-.177	**.540*** **	1	-	-	-	-
Down	**-.526*** **	**-.413*** **	**-.678*** **	**-.614*** **	-.165	**.662*** **	**.540*** **	1	-	-	-
Loneliness	**-.447*** **	**-.271***	**-.365****	**-.429*** **	**-.511*** **	**.499*** **	**.429*** **	**.448*** **	1	-	-
Guilt	-.071	.083	-.176	-.211	**-.264***	.236	.223	.141	**.437*** **	1	-
Stress	**-.266***	-.188	**-.568*** **	**-.343****	-.035	**.418*** **	**.595*** **	**.596*** **	**.247***	.163	1

Note: ***=*p*<0.05, ****=*p*<0.01, *****=*p*<0.001

Having examined the association between each of the PA and NA variables, further analysis was conducted across each affect scale to assess the internal consistency of each item. Results from these analyses highlighted a Cronbach's alpha of 0.81 for the PA items. However, when safety was removed from the PA item list an improved Cronbach's alpha of 0.86 was observed. Due to the lack of significant positive associations with other items across the PA variables, and the improvement on the internal consistency of the PA scale, safety was dropped from the list contributing to the PA dimension and excluded from any further downstream analysis.

When examining the NA variables, a Cronbach's alpha of 0.87 was observed. However, removing the guilt variable, which showed poor correlation between NA items, as well as the loneliness item, which although showed good between item correlations resulted in improved internal consistency producing a Cronbach's alpha of 0.88. It is thought that whilst loneliness was well correlated, in the expected directions, with both PA and NA items, the concept of loneliness is highly subjective and context dependant, leading to the resulting impact on the internal consistency of the scale. Furthermore, both guilt and loneliness had considerably weaker item-rest correlations of 0.56 and 0.52 respectfully when compared to the other items which ranged from 0.72 for stress to 0.75 for tense. As a result, both guilt and loneliness were dropped from the list contributing to the NA dimension and consequently removed from further downstream analysis.

3.3.3. Reliability analysis – Measures of cognitive biases

Following this, the reliability of the cognitive bias measures was also assessed. Three assessments of reliability were conducted across each of the cognitive biases and their positive and negative components. Firstly, two tests of split half reliability were conducted across each of the cognitive biases using the Spearman-Brown Prophesy Estimate method, examining the correlations between the responses given for the odd and even positive items and negative items, which were equal in numbers. For the dot probe task (DPT), used to measure attention bias, the Spearman-Brown corrections of the split-half correlations revealed no significant correlation for the two halves of the attention bias score (r=.152, p=.126), or the positive (-.180, p=068) and negative (r= -.094, p=.344) components. Following this, the Spearman-Brown Prophesy Reliability Estimate was calculated as: 2 x r(rho) / (1+r(rho)). This revealed low internal consistencies for both the attention bias score (r=*.263*) and the positive (r=*-.439*) and negative (r=*-.208*) components. Lastly, a test of average intraclass correlation coefficients (ICC) also

revealed non-significant findings across attention bias scores (ICC=.263, 95%CI=-.090-.502, F(102.0, 102.0)=1.36, *p*=.063) and both positive (ICC=-.437, 95%CI=-1.123-.027, F(102.0, 102.0)=0.69, *p*=.966) and negative (ICC=-.208, 95%CI=-.789-.183, F(102.0, 102.0)=0.83, *p*=0.829) components of the measure.

The split-half reliability for the Self-Referential Encoding Task (SRET) measure of memory bias revealed that whilst the memory bias score did not reach statistical significance (*r*=.169, *p*=.095), significant correlations were found for *positive memory bias* (*r*=.201, *p*=.041) and *negative memory bias* (*r*=.271, *p*=.005) components of this measure. However, Spearman-Brown Prophesy Reliability Estimate revealed low internal consistency for *memory bias* (*r=.289*), and both the *positive memory bias* (*r=.335*), and *negative memory bias* (*r=.427*) components. The average ICC of the SRET task also revealed the memory bias score to be non-significant (ICC=.276, 95%CI= -.076-.514, F(98.0, 99.0) = 1.38, *p*=.055), however only marginally so, with both *positive memory bias* (ICC=.339, 95%CI=.026-.551, F(103.0, 104.0)=1.51, *p*=.018), and *negative memory bias* (ICC=.358, 95%CI=.055-.564, F(103.0, 104.0)=1.56, *p*=.012) shown to be significant.

The split-half reliability regarding the Scrambled Sentence Task (SST) measure of interpretation bias revealed significant correlations for the interpretation bias score (*r*=.617, *p*=<.000), as well as the positive interpretation bias (*r*=.532, *p*=<.000) and negative interpretation bias components (*r*=.653, *p*=<.000). The Spearman-Brown Prophesy Reliability Estimate also demonstrated substantial internal consistency across the interpretation bias scores (*r= .763*) and both the positive interpretation bias (*r= .694*), and negative interpretation bias (*r= .790*) components. The average ICC of the SST was also significant for the interpretation bias score (ICC=.591, 95%CI=.445-.706, F(96.0, 97.0)=3.89, *p*=<.000) and the positive interpretation bias (ICC=.434, 95%CI=.258-.582, F(96.0, 97.0)=2.53, *p*=<.000) and negative interpretation bias (ICC=.655, 95%CI=.526-.755, F(96.0, 97.0)=4.81, *p*=<.000) components.

As a result of these analyses (summarised in **Table 3.4**) and the low internal consistency of the DPT, as well as the non-significant findings demonstrated by the split-half reliability analysis and ICC tests across all aspects of the measure, attention bias was dropped from any further analysis. However, although memory bias did show similar low internal consistency, the positive and negative memory bias components were significant in split-half reliability analysis

and ICC tests, with the memory biases score trending towards significance in the ICC test. Therefore, memory bias was tentatively included in further analysis with any significant results been interpreted with this in mind.

Table 3.4. Summary of split half, Spearman-Brown, and average ICC reliability tests.

Cognitive biases	**Split half**	**Spearman-Brown**	**Average ICC**
Attention bias	.152	.263	.263
Positive attention bias	-.180	-.439	-.437
Negative attention bias	-.094	-.208	-.208
Memory bias	.169	*.289*	.276
Positive memory bias	**.201***	*.335*	**.339***
Negative memory bias	**.271***	*.427*	**.358***
Interpretation bias	**.617***	.763	**.591***
Positive interpretation bias	**.532***	.694	**.434***
Negative interpretation bias	**.653***	.790	**.655***

Note: *=p**<0.05

3.3.4. Effect of cognitive biases on daily life level of affect

Linear mixed-effect models were used to assess the main effects of cognitive biases on daily life levels of PA and NA. The results regarding these analyses are shown in **Table 3.5.**

Table 3.5. Displaying beta coefficients, confidence intervals and p-values from mixed model analysis regarding the main effects of cognitive biases in interpretation and memory on positive and negative affect.

Cognitive biases	**Positive Affect**			**Negative Affect**		
	β	95% CI	*P*	β	95% CI	*P*
Memory bias	-.09	(-.21-.02)	.120	.01	(-.14-.16)	.903
Interpretation bias	-.17	(-.28--.05)	**.003* (.007)****	.15	(-.00-.29)	.051

Note: Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

As demonstrated in **Table 3.5** interpretation bias was found to have a significant negative association with PA, which also survived correction for multiple testing. This suggests that having a more negative interpretation bias resulted in decreasing PA levels within the sample.

When examining the positive and negative components of interpretation bias it becomes clear that the negative effect of interpretation bias on levels of PA was driven by the negative component of interpretation bias (*negative interpretation bias*). Although the positive component of interpretation bias (*positive interpretation bias*) was observed as having a significant positive effect on PA, the association did not survive multiple testing correction (β=0.12, 95%CI=0.00-0.24, p=0.042, FDR=0.084). However, the negative association between negative interpretation bias and PA did remain significant following multiple testing correction (β=-0.18, 95%CI=-0.29--0.07, p=0.001, FDR=0.004) driving the initially observed significant negative effect.

3.3.5. Effect of cognitive biases on affect variability

Correlation analysis regarding the standard deviations of each of the affect variables in relation to each of the cognitive biases was conducted to examine the variability of both PA and NA over the seven days of experience sampling in keeping with previous research (Komulainen et al., 2014). The results of the analyses can be found in **Table 3.6**.

Table 3.6. Displaying results of the correlation analysis regarding the impact of cognitive biases in interpretation and memory on the variability of positive and negative affect.

Cognitive biases	Positive Affect	Negative Affect
Memory bias	r= -0.099, p=0.401	r=-0.053, p=0.651
Interpretation bias	r=-0.021, p=0.862	r=0.002, p=0.989

The results in **Table 3.6** revealed no significant correlation between any of the cognitive biases tested and the PA and NA standard deviations, suggesting that there is no effect of cognitive biases on the variability of PA and NA across seven days of experience sampling.

3.3.6. Effect of cognitive biases on daily life context

In order to assess the main effect of each cognitive bias on each daily life context variable linear mixed-models and logistic regression analysis was conducted. The results from these analyses are shown in **Table 3.7**.

Table 3.7. Displaying beta coefficients, 95% confidence intervals and *p*-values from mixed model and logistic regression analysis regarding main effects of cognitive biases in interpretation and memory, on all context variables.

Cognitive biases		**Quality of previous event**	**Quality of current activity**	**Quality of solitude**	**Quality of social interaction**
Memory bias	ß	-.01	-.01	.18	-.08
	95% CI	(-.11-.08)	(-.12-.10)	(-.33-0.70)	(-.46-.30)
	P	.760	.835	.492	.682
Interpretation bias	ß	-.11	-.11	.23	-.39
	95% CI	(-.20--.02)	(-.21--.00)	(-.28-.75)	(-.74--.04)
	P	**.021* (.041)****	**.048*** (.096)	.373	**.027*** (.054)

Note: Results pertaining to the variable 'Quality of previous event' and 'Quality of current activity' represent outputs from mixed model analysis. Those for 'Quality of solitude' and 'Quality of social interaction' represent outputs from logistic regression due to the binary response given to obtain the measures. The random effects of time were not included in the logistic regression models due to missing data. Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

Results revealed interpretation bias as having significant negative associations with the quality of previous event, the quality of the current event, and the quality of social interaction at the time of the notification. However, only the result regarding the quality of the previous event survived correction for multiple testing. This result suggests that having a more negative interpretation bias has a negative impact on the perceived quality of previous events, effectively reducing the enjoyment of the events experienced prior to the notification.

When exploring the positive and negative components of interpretation bias (*positive and negative interpretation bias*), both were observed as having a significant association with the quality of the previous event. That is, positive interpretation bias was shown as having a positive association with the previous events' quality (β=0.09, 95%CI=0.00-0.19, p=0.049, FDR=0.049), thereby increasing the perceived quality of the previous event. Conversely, negative interpretation bias had the opposing effect with a negative association observed (β=-0.12, 95%CI=-0.21--0.03, p=0.009, FDR=0.018), indicating a decrease in the perceived quality of the previous event. Here, it seems that despite the presence of a positive interpretation bias, the negative effect of a negative

interpretation bias prevailed, with greater significance and effect, buffering against the positive interpretation bias and driving the initial association with the quality of previous event.

3.3.7. Effect of daily life context on affect

To assess the main effect of daily life contexts on levels of affect the same linear mixed-effect models were run examining the quality of each context variable and their effect on PA and NA. To allow the coefficients from the analysis to be more intuitive, results were reported with lower quality of daily events on level of NA and high quality of daily events on level of PA. Results are displayed in **Table 3.8**.

Table 3.8. Displaying beta coefficients, 95% confidence intervals and *p*-values from mixed model analysis regarding the main effects of daily life contexts on positive and negative affect.

Daily life contexts	**Positive Affect**			**Negative Affect**		
	ß	95% CI	*P*	ß	95% CI	*P*
Quality of previous event	.54	(.51-.57)	**<.001**	.37	(.34-.40)	**<.001**
Quality of current activity	.54	(.51-.57)	**<.001**	.39	(.36-.42)	**<.001**
Quality of solitude	.06	(-.00-.11)	.057	.04	(-.01-.09)	.159
Quality of social interaction	.35	(.30-.40)	**<.001**	.22	(.18-.26)	**<.001**

As can be seen in **Table 3.8** the quality of the previous event had a significant positive association with both PA and NA levels that survived correction for multiple testing. Specifically, perceiving a previous event as positive was associated with an increase in PA, whilst perceiving a previous event as negative was associated with increases in NA. This pattern was also true, to a very similar extent, for the quality of the current activity, as it was shown to have a significant positive association that also survived multiple testing correction with both PA and NA. Again, perceiving a current activity as positive increased PA, whilst experiencing a current activity as negative increased NA. However, as can be seen, the effects of a negative previous event and negative current activity on NA, although similar to each other, were considerably smaller than the effects of a positive previous event and positive current activity on PA. The quality of social interaction was also found to have a significant positive association with both PA and NA, again remaining significant following multiple testing correction. That is, being involved in social interaction perceived to be positive at the time of the notification was seen to increase levels of

PA, whilst involvement in negative social interaction increased levels of NA. Quality of solitude had no significant impact on either PA or NA.

3.3.8. Effect of cognitive biases on reward reactivity (positive affect)

To examine whether the effects of daily life contexts on PA and NA was moderated by cognitive biases, interactions between each of the cognitive bias variables and each of the contexts were assessed. First, the interactions between cognitive biases and context on PA was examined, with results regarding previous event, current activity and quality of present company (positive solitude and positive social interaction) presented in **Table 3.9**. Furthermore, in accordance with **Table 3.8** regarding the main effects of daily life context on affect, the results in **Tables 3.9** were reported as the interaction between cognitive biases and higher rated quality of daily events on level of PA.

Table 3.9. Displaying results from mixed model analyses examining the interactions between each of the cognitive bias and each subjectively rated context on positive affect.

Contexts	**Memory bias**			**Interpretation bias**		
	ß	95% CI	*P*	ß	95% CI	*P*
Positive previous event	-.01	(-.04-.02)	.522	-.04	(-.07--.01)	**.010* (.021)****
Positive current activity	0	(-.04-.03)	.815	-.07	(-.10--.03)	**$8.42x10^{-5}$*($1.68x10^{-4}$)****
Positive solitude	.04	(-.02-.10)	.221	.11	(.05-.17)	**.001* (.001)****
Positive social interaction	.01	(-.04-.07)	.597	.01	(-.04-.05)	.813

Note: Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

As is shown in **Table 3.9** interpretation bias was observed to have significant interactions with both positive previous event, and positive current activity, both of which had a negative direction of effect and survived multiple testing correction. Here, in both cases, despite experiencing a positive previous event, and positive current activity, the presence of a negative interpretation bias resulted in a decrease in PA with the effect of the environment failing to buffer against a negative interpretation bias. There was also a significant interaction between interpretation bias and experiencing positive solitude which had a positive effect on levels of PA and remained significant following corrections for multiple testing. This finding suggests that for

those with a more negative interpretation bias, being alone, and experiencing it as positive (positive solitude), results in an increase in PA.

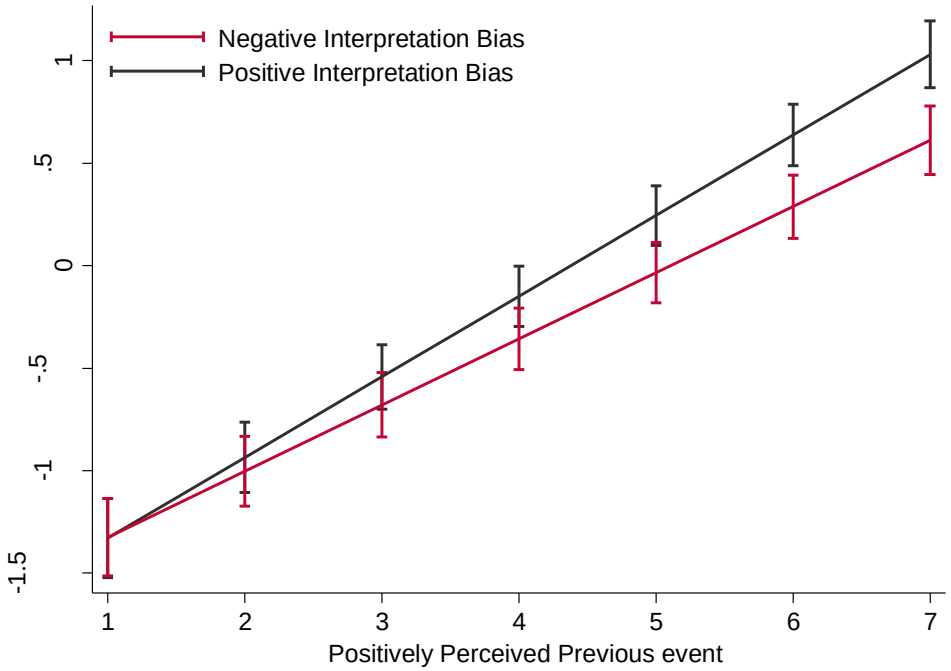
These significant interactions were then assessed further by examining the positive and negative components of interpretation bias. Here, both positive and negative interpretation bias components were found to be significant. There were significant interactions between *negative interpretation bias* and both positive previous event (β=-0.04, 95%CI=-0.07--0.01, p=0.019, FDR=0.019) and positive current activity (β=-0.06, 95%CI=-0.09--0.03, $p=4.2\text{x}10^{-4}$, $\text{FDR}=4.2\text{x}10^{-4}$), both of which had negative effects on levels of PA. Conversely, there was also a significant interaction between *positive interpretation bias* and both positive previous event (β=0.05, 95%CI=0.02-0.08, p=0.001, FDR=0.002), and positive current activity (β=0.07, 95%CI=0.03-0.10, $p=7.33\text{x}10^{-5}$, $\text{FDR}=1.46\text{x}10^{-4}$), both having a positive effect on levels of PA. Results here suggest that having a negative interpretation bias buffers against the effects of a positive interpretation bias and positive previous event and current activity to reduce levels of PA.

Both positive and negative components of interpretation bias were found to have a significant interaction with being alone by choice (positive solitude) to a very similar extent, albeit with opposite directions of effect. *Positive interpretation bias* was found to have a significant interaction with positive solitude (β=-0.1, 95%CI=-0.16--0.03, p=0.002, FDR=0.002), with a negative direction of effect, suggesting that having a *positive interpretation bias* and experiencing positive solitude has a negative impact, decreasing levels of PA. Conversely, *negative interpretation bias* was shown as having a significant interaction with positive solitude (β=0.11, 95%CI=0.05-0.17, p=0.001, FDR=0.001), with a positive effect on PA to the same extent as interpretation bias itself. Whilst unexpected this could suggest that those with a negative interpretation bias are more likely to choose to be alone and benefit from the experience with increased PA, while those with a positive interpretation bias choosing to be alone are unable to benefit from the solitude. Furthermore, whilst it seems evident that having a more negative interpretation bias buffers against the apparent negative effects of a positive interpretation bias, this was only true in the context of choosing to be alone (positive solitude).

Simple slope analysis was then conducted to examine the significant interactions in more detail, assessing those with a more positive and those with a more negative bias, as defined by upper and lower quartiles of interpretation bias score. Analysis of the simple slopes regarding the

interaction between interpretation bias and positive previous event on PA revealed that those with a more positive interpretation bias benefited considerably more from a positive previous event (β=0.60, 95%CI=0.53-0.66, *p*=<0.001), compared to those with a more negative interpretation bias (β=0.46, 95%CI=0.40-0.52, *p*=<0.001), although both had significant positive effects. These effects are illustrated below in **Figure 3.1**.

Figure 3.1. Margins plot displaying the predicted effects of positively perceived previous events on levels of PA for those with a more positive and more negative interpretation bias.



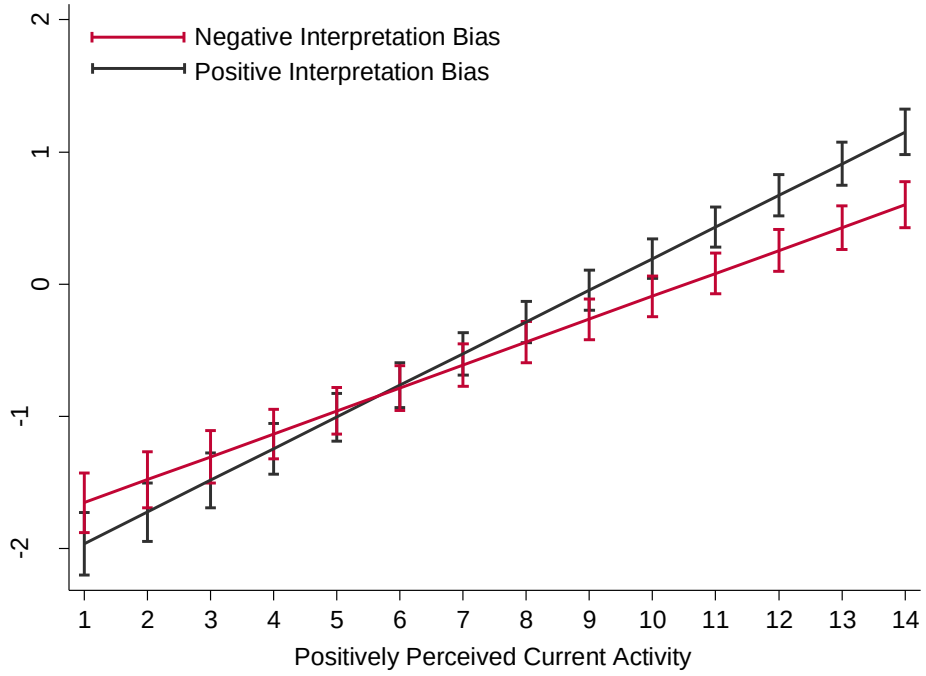
Note*:* The red line represents those with interpretation bias scores in the upper quartile (more negative bias), with the black line representing those with interpretation bias scores in the lower quartile (more positive bias).

Figure 3.1 illustrates the effect of positively perceived previous events on PA in those with a more positive and negative interpretation bias demonstrating no significant difference in levels of PA when perceived previous events are reported as "very unpleasant". However, despite both effects being significant, as the perception of previous events becomes more positive those with a more positive interpretation bias benefit from a significantly greater increase in PA compared to those with a more negative interpretation bias.

Simple slope analysis regarding the interaction between interpretation bias and positive current activity on PA revealed a similar picture. Specifically, individuals with a more positive

interpretation bias experienced considerably larger increases in PA as a result of a positive current activity (β=0.62, 95%CI=0.55-0.68, *p*=<0.001), in comparison to individuals with more negative interpretation biases (β=0.42, 95%CI=0.35-0.48, *p*=<0.001), although, once again, both had significant positive effects. These effects are illustrated below in **Figure 3.2**.

Figure 3.2. Margins plot displaying the predicted effects of positively perceived current activity on levels of PA for those with a more positive and more negative interpretation bias.



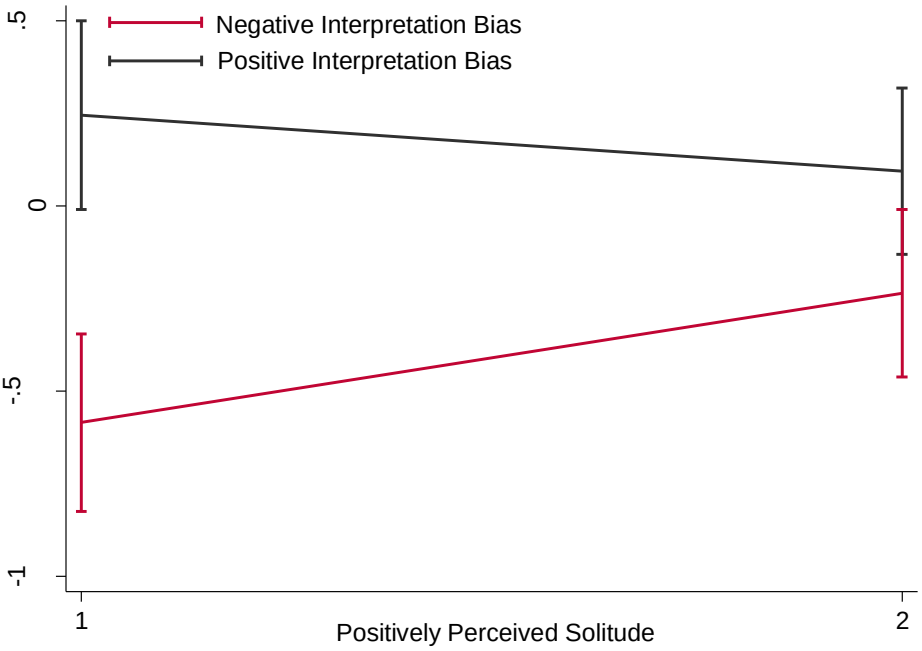
Note: The red line represents those with interpretation bias scores in the upper quartile (more negative bias), with the black line representing those with interpretation bias scores in the lower quartile (more positive bias).

Figure 3.2 illustrates a cross-over interaction regarding the effect of positively perceived current activity (the sum of both enjoyment and ability) on PA in those with a more positive and negative interpretation bias. Here, those with a more negative interpretation bias are shown as having higher levels of PA compared to those with a more positive interpretation bias when reporting current activities as most negative. However, a steeper slope is observed for those with a more positive interpretation bias as the perception of current activities are reported to be more positive, with levels of PA between the two groups becoming more similar. However, higher levels of PA are observed for those with a more positive interpretation bias when reporting current

activities as more positive. This gain in levels of PA for those with more positive interpretation bias becomes significantly greater than those with a more negative interpretation bias as reports regarding current activities approach most positive.

Simple slopes analysis of the significant interaction between interpretation bias and being alone by choice (positive solitude) on PA revealed that the initial interaction was unexpectedly driven by individuals with a more negative bias, yet resulted in an increase in PA. Specifically, having a more negative interpretation bias and being alone by choice had a significant positive effect, increasing levels of PA (β=0.16, 95%CI=0.05-0.28, *p*=0.005). However, for those with a more positive interpretation bias who were alone by choice a non-significant negative association was observed (β=-0.08, 95%CI=-0.23-0.07, *p*=0.314). This suggests that having a negative interpretation bias and choosing to be alone has a protective effect, and benefits levels of PA, whereas having a more positive interpretation bias in the same environment has the opposite effect, although not significantly. These effects are illustrated below in **Figure 3.3**.

Figure 3.3. Margins plot displaying the predicted effects of positively perceived solitude on levels of PA for those with a more positive and more negative interpretation bias.



Note: The red line represents those with interpretation bias scores in the upper quartile (more negative interpretation bias), with the black line representing those with interpretation bias scores in the lower quartile (more positive bias). On the x-axis, 1=alone at notification, whilst 2=alone by choice.

Figure 3.3 illustrates the effect of being alone by choice (positive solitude) on levels of PA in those with more positive and negative interpretation bias. Here, those with a more negative interpretation bias who were experiencing positive solitude demonstrate a significant increase in levels of PA, whilst those with a more positive interpretation bias show a non-significant reduction in PA when experiencing positive solitude.

3.3.9. Effect of cognitive biases on stress reactivity (negative affect)

The same analysis was then conducted for the same interaction effects on NA, with results regarding negative previous event and current activity as well as those regarding negative solitude and social interaction presented in **Table 3.10**. Conversely to above, results were reported as the interaction between cognitive biases and lower quality of daily events on level of NA.

Table 3.10. Displaying results from mixed model analyses examining the interactions between each of the cognitive bias and each subjectively rated context on negative affect.

Contexts	**Memory bias**			**Interpretation bias**		
	ß	95% CI	*P*	ß	95% CI	*P*
Negative previous event	-.02	(-.05-.02)	.332	-.01	(-.04-.02)	.487
Negative current activity	-.01	(-.04-.02)	.527	-.03	(-.06--.00)	**.028*** (.056)
Negative solitude	.02	(-.03-.08)	.460	.07	(.01-.13)	**.022* (.043)****
Negative social interaction	.03	(-.02-.08)	.196	.02	(-.01-.06)	.216

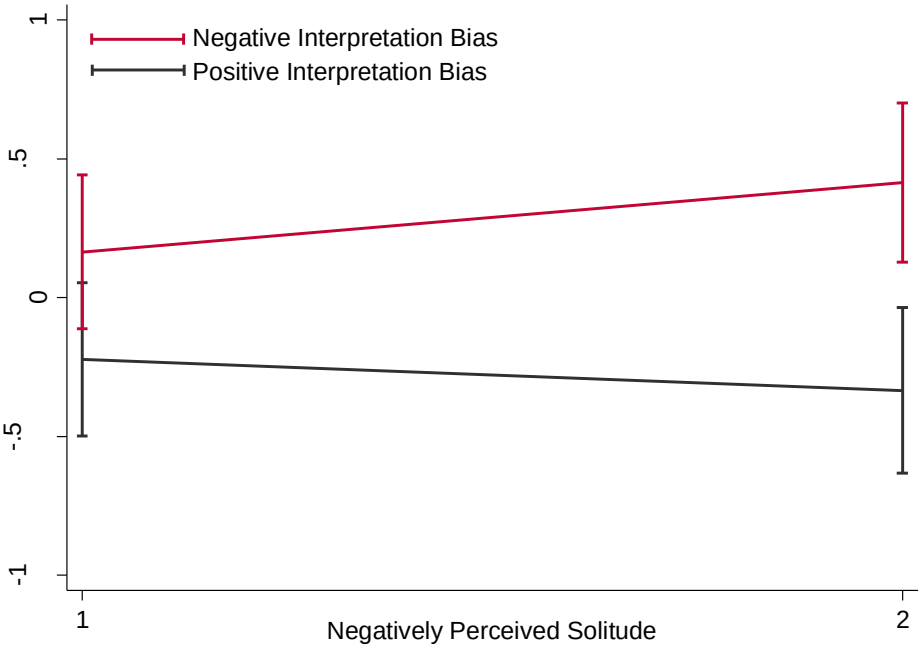
Note: Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

Results displayed in **Table 3.10** highlight an unexpected significant interaction between interpretation bias and negative current activity with a negative effect on levels of NA. However, this did not remain significant following multiple testing correction suggesting that the initial significant findings may have been spurious and the result of a type I error, or possibly did not reach significance due to a lack of statistical power. Despite this, there was a significant interaction observed between interpretation bias and being alone *not* by choice (negative solitude) that had a positive effect on levels of NA. This finding suggests that having a more negative interpretation bias and perceiving time spent alone as negative increases levels of NA.

When examining the positive and negative components of interpretation bias (*positive and negative interpretation bias*), significant interactions with being alone *not* by choice (negative solitude) on levels of NA were observed for both. As expected, there was a significant interaction between *positive interpretation bias* and negative solitude with a positive effect on levels of NA (β=-0.07, 95%CI=-0.12--0.01, p=0.024, FDR=0.025), and a significant positive interaction between *negative interpretation bias* and negative solitude on levels of NA (β=0.07, 95%CI=0.01-0.13, p=0.025, FDR=0.025). However, as can be seen, both findings were very similar albeit with opposing directions of effect. Despite this, it was the effect of the interaction between *negative interpretation bias* and negative solitude that prevailed, buffering against the effects of the interaction between positive interpretation bias and negative solitude.

Simple slope analysis regarding the significant interaction between interpretation bias and being alone *not* by choice (negative solitude) highlighted those with a negative interpretation bias as driving the initial interaction. That is, having a more negative interpretation bias and being alone *not* by choice had a significant positive effect, thereby increasing levels of NA (β=0.12, 95%CI=0.01-0.23, *p*=0.028). Conversely, having a more positive interpretation bias and being alone *not* by choice had a negative effect on levels of NA, although this was non-significant (β=-0.06, 95%CI=-0.20-0.07, *p*=0.348). This suggests that having a more positive interpretation bias may buffer against the effect of negative solitude to protect levels of affect, whilst having a more negative interpretation bias and experiencing negative solitude increases level of NA. These effects are illustrated below in **Figure 3.4**.

Figure 3.4. Margin plot displaying the predicted effects of negatively perceived solitude on levels of NA for those with a more positive and more negative interpretation bias.



Note: The red line represents those with interpretation bias scores in the upper quartile (more negative interpretation bias), with the black line representing those with interpretation bias scores in the lower quartile (more positive interpretation bias). On the x-axis, 1=alone at notification, whilst 2=*not* alone by choice.

Figure 3.4 illustrates the effect of being alone *not* by choice (negative solitude), on levels of NA in those with more positive and negative interpretation bias. Here, a significant increase in NA is observed for those with a more negative interpretation bias when experiencing solitude as negative, whilst a non-significant reduction in NA is seen for those with a more positive interpretation bias when experiencing solitude as negative.

3.4. Discussion

The aim of the current study was to investigate the effect of cognitive biases on levels of PA and NA in daily life, as well as their effect on both positively and negatively perceived day-to-day contexts over a 7-day period of experience sampling. More specifically, the current study assessed the association between cognitive biases in memory and interpretation and daily life levels of affect. Following this, the effect of the same cognitive biases on affect variability was examined, as well as their effect on perceived quality of daily life contexts. Lastly, the effects of both memory and interpretation bias as moderating the relationship between both positively and negatively perceived daily environmental contexts on levels of affect were assessed. The hypotheses regarding these aims and results pertaining to them are discussed below.

3.4.1. Effect of cognitive biases on daily life levels of affect

It was the hypothesis of the current study that cognitive biases measured at baseline would have a significant effect on levels of affect, as well as affect variability throughout the seven-day period of experience sampling. In line with the hypothesis interpretation bias was found to have a significant negative effect on PA, but not NA, reducing PA as a result of a more negative interpretation bias. Further analysis of the positive and negative components of interpretation bias demonstrated that despite both components having significant associations with PA, albeit in opposing directions of effect, it was clear that the negative interpretation bias component was driving the association, having a far greater effect on levels of PA. However, contrary to expectations there were no significant associations observed between cognitive biases in memory or interpretation and affect variability. This suggests that whilst having a negative interpretation bias was associated with lower levels of PA, neither a negative memory nor interpretation bias was associated with changes in affect levels over one week.

To date, there has been little research examining the effects of cognitive biases on levels of affect, especially using ESM designs. However, a previous ESM study assessing the effect of the personality traits on levels of affect has demonstrated neuroticism as having a negative impact on PA traits and trait variability (Komulainen et al., 2014). Another longitudinal study has also demonstrated an association between attentional processing bias and negative mood state in response to stress using a measure of state anxiety (Fox et al., 2010). However, the current study

provides evidence, for the first time, that a more negative interpretation bias is associated with reduced levels of PA in the course of daily life, but not variability.

There has been a considerable amount of research highlighting the protective effect of PA emotions and reward against the effects of stress (Bijttebier, Raes, Vasey, & Feldman, 2012; Corral-Frías, Nadel, Fellous, & Jacobs, 2016; Corral-Frías et al., 2015; Geschwind et al., 2010; Nikolova, Bogdan, Brigidi, & Hariri, 2012; Ryba & Hopko, 2012; Vythilingam et al., 2009). In the most recent of these studies (Corral-Frías et al., 2016), examining the effect of reward sensitivity on levels of affect, researchers assessed 140 healthy students for resiliency and sensitivity to reward. Trait resilience was assessed using a self report 25 item resilience questionaire (Wagnild & Young, 1993), with three Behavioral Activation Scale (BAS) subscales (Carver & White, 1994), and a computer based 90-trial monetary incentive delay task (Knutson, Westdorp, Kaiser, & Hommer, 2000), to assess sensitivity to reward. Participants were pseudo-randomly assigned to either an experimentally induced stress or control group and presented with either the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) or the Placebo Trier Social Stress Test (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009). Self-report measures of affect were assessed before, during and after the stress task using the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988). Their findings revealed signifcant increases in NA and decreases in PA in participants both during and after experimentally incuded stress. Furthermore, they demonstrated that higher levels of reward sensitivity were associated with higher levels of PA regardless of stress exposure, and that reward sensitivity successfully predicted levels of PA following exposure to threat, as it moderated the relationship between PA and stress exposure.

In light of such findings, and the findings of the current study it could be suggested that interpretation bias represents a potential mechanism by which reward sensitivity and PA are regulated. That is, whilst a more negative interpretation bias was not associated with variability in affect levels, it was associated with lower levels of PA suggesting that if a negative interpretation bias were modified to be more positive it may also increase PA with a similarly stable effect. This suggestion, and the current findings regarding negative interpretation bias and PA, are also in line with research examining the effects of modifying interpretation bias, on both emotional reactivity (E. Watkins et al., 2008) and mood (Lothmann et al., 2011). For example, to examine what effect manipulating interpretation bias has on mood, Lothmann et al. (2011) randomly selected 82

healthy 13-17-year olds into either a positive or negative cognitive bias modification (CBM) training condition. In the training phase participants were presented with written ambiguous scenarios with the last word of each sentence left incomplete. They were required to complete each sentence and resolve the ambiguity of the scenarios, which could only be done as positively or negatively depending on the condition. The testing phase require participants to read 10 ambiguous scenarios before being presented with sentences that they were asked to rate in accordance with how similar they were to the ambiguous scenarios they had just been presented with. Mood changes were assessed immediately before and after both training and testing phases by means of 12 visual analogue scales (VAS) which measured levels of PA and NA. Results showed not only that CBM techniques such as this were able to successfully manipulate interpretation bias in a desired direction, but also that modifications in interpretation bias had a significant effect on levels of both PA and NA. Specifically, those in the positive condition endorsed more positive interpretations of the test scenarios than negative, whist the inverse was observed for those in the negative condition. The mood of those in the positive condition demonstrated a significant drop in NA whilst those in the negative condition were found to show a significant drop in PA.

This was the first study to examine this effect in adolescents. However, other interpretation bias modification (CBM-i) studies have also reported similar findings in both healthy adult participants (Mathews & Mackintosh, 2000), as well as those suffering from affective disorders such as depression (Joormann et al., 2015; LeMoult et al., 2018). This evidence combined with that from the current study further confirms associations between interpretation bias and mood. Furthermore, these combined findings also offer further support for interpretation bias as a potential mechanism impacting on stable, but *not* variable levels of PA, as well as the potential benefits of increasing a positive interpretation bias using techniques such as CBM-i. However, as studies in this area are lacking more research is required to further assess and replicate this association and investigate further the protective benefits of a positive interpretation bias including its effects of affective states.

3.4.2. Effect of cognitive biases on daily life contexts

It was also the hypothesis of the current study that there would be a significant main effect of cognitive biases on the perceived quality of daily life contexts. In keeping with this expectation, a significant negative association was observed between interpretation bias and the quality of

previous events. This suggests that individuals with a more negative interpretation bias report previous events as lower in quality, or more negative, than those with a more positive interpretation bias. This was further confirmed when the individual positive and negative components of interpretation bias were examined in more detail revealing a very similar significant negative effect for negative interpretation bias, and no significant effect of positive interpretation bias.

To date, there has been no previous ESM research examining the effect of cognitive biases on daily life, and only a limited body of research examining the effect of cognitive biases on levels of affective states. Furthermore, the majority of this research has focused on attention biases using cross-sectional experimental designs (Clasen et al., 2013; LeMoult et al., 2013), with only a single study having assessed these effect longitudinally (Fox et al., 2010). Research in this area regarding the effect of interpretation bias in healthy individuals tends to focus on what effect modifying interpretation bias has on elements of emotional reactivity (Hoppitt, Mathews, Yiend, & Mackintosh, 2010; Mathews & Mackintosh, 2000; Tran, Siemer, & Joormann, 2011; Wilson, MacLeod, Mathews, & Rutherford, 2006). Such CBM-i research assesses reactivity to laboratory-based stressors designed to work as a proxy for emotional responses in daily life. In one such study Wilson et al. (2006) investigated the effects of modifying interpretation bias on anxiety vulnerability in 48 healthy individuals by inducing the interpretation of ambiguous information as having either a threatening or non-threatening meaning. Following the interpretation bias training, participants were shown videos of real-life emergency scenarios in which an individual is subjected to injury, but eventually rescued. Results demonstrated that the modification of interpretation bias had a significant impact on the participants emotional reactivity to the videos, inducing the intended training effects by increasing state anxiety in the negative, but not positive training group. In a separate study these effects have also been shown to persists for a least a day after modification, influencing reactions, in accordance with the training, to real-life accidents across varying contexts shown on videos (Mackintosh, Mathews, Yiend, Ridgeway, & Cook, 2006).

Whilst the current study did not modify interpretation bias, the results can be said to be in line with that of the CBM-i research highlighted above, as a more negative interpretation bias increased the perception of previous events as having less quality (more negative), compared with a more positive bias. These findings confirm the association between a negative interpretation bias and perceiving events or scenarios as more negative and extends further by demonstrating these

effects longitudinally in real daily life, providing greater ecological validity for the association. Moreover, like with the effect of interpretation bias on daily levels of PA, the CBM-i research highlighted above has further demonstrated that interpretation bias can be modified, and that it can have a significant and lasting effect on the interpretation of events. CBM-i techniques could therefore serve as two-fold, modify a negative interpretation bias to be more positive, and increasing levels of PA. This, by extension could also be said to demonstrate interpretation bias as a causal mechanism impacting on both levels of PA and perception of daily events. However, further ESM research is required to replicate these findings as this is the first time these effects have been shown in such an ecologically valid setting.

3.4.3. Effect of daily life context on affect

The current study also expected that the perceived quality of the daily life contexts would have a significant main effect in levels of PA and NA independently of cognitive biases, across the seven-day ESM testing period. This hypothesis was confirmed with analysis revealing highly significant association between quality of previous events, quality of current activity and quality of social interaction, but not quality of solitude, and levels of both PA and NA. Results also revealed a consistent trend regarding the effect of the significant environmental contexts, with the significant contexts having a stronger effect on PA in all cases.

Whilst the same environmental effects have been examined before in a previous ESM paper by Komulainen et al. (2014), to which this study is a part replication, their main effects were not interpretable outside of the interaction analysis and were not reported elsewhere. This was also the case for the ESM study by Hundt et al. (2013) discussed in the introduction and is a persistent issue regarding many studies assessing interaction effects. However, the current findings join a number of studies that have demonstrated the significant main effects of environmental factors on levels of affective states. For example, a previous diary study has demonstrated strong effect of daily positive events on levels of PA and similarly strong effects of negative events on NA (Gable, Reis, & Elliot, 2000). In more recent studies experimentally induced stress has been demonstrated as increasing NA (Bogdan & Pizzagalli, 2006; Corral-Frías et al., 2016) and reducing PA (Corral-Frías et al., 2016).

These studies, along with many others, highlight the environment as having strong effects on affective states, with effect sizes often suggesting that environmental effects represent the most important independent factors impacting on levels of affect. The finding from the current study can be seen as in line with these associations further confirming the importance of the environment on levels of affect. However, future ESM research, reporting the main effects of these environmental measures, is needed to further confirm these findings.

3.4.4. Effect of cognitive biases on affect reactivity

The current study had hypothesized that cognitive biases would have a significant impact on daily levels of affect in response to positive and negative daily life contexts. In keeping with this hypothesis several associations were observed regarding the interaction between interpretation bias and both positive and negative daily life contexts on levels of affect, but not for memory bias. Specifically, interpretation bias had significant interactions with positive previous events, positive current activity, and positive solitude (choosing to be alone) on levels of PA, and with negative solitude (not alone by choice) on levels of NA.

The most noticeable elements of these findings are firstly, that interpretation bias clearly plays an instrumental role in affect reactivity throughout the course of daily life, and secondly that its effect is far more significant and broader in impact for PA compared to NA. For example, the interaction effects of interpretation bias on PA in the context of positive previous event and positive current activity demonstrates that a negative interpretation bias overrides the effects of past and present positive environments to reduce levels of PA. This is particularly interesting as the main effects of these specific environmental measures were highly significant, with strong positive directions of effect on levels of PA. Furthermore, the buffering effect of a negative interpretation bias against the positive effect of a positive previous event and current activity was specific to a reduction of PA. That is, no significant interactions were observed between having a more negative interpretation bias and either negatively report previous event or current activity on levels of NA. Further analysis of the positive and negative components of interpretation bias revealed that these interactions were driven by a negative interpretation bias. Furthermore, the negative effect of a negative interpretation bias also buffered against the significant positive effects of both a positive interpretation bias and positive environments to reduce levels of PA. Simple slope analysis of the upper and lower quartiles of interpretation bias further confirmed these

findings demonstrating both positive previous event and current activity as having much less of a positive effect on those with a more negative interpretation bias, in comparison to those with a more positive bias.

Past ESM research has demonstrated significant interaction between the 'Big Five' personality traits and perceived negative events and activities that significantly increased levels of the NA trait sadness (Komulainen et al., 2014). Another ESM study has also shown sensitivity to reward as being associated to PA, and sensitivity to punishment as associated with NA. Sensitivity to punishment was also associated with less reduction of NA, and less increase in PA when perceiving an event as positive compared to individuals with lower sensitivity to punishment (Hundt et al., 2013). However, the current findings represent the first time a negative interpretation bias has been shown to negatively impact on levels of PA in the course of positive daily life events using an ESM design.

The importance and protective effect of PA emotional traits against stress and their association with reward sensitivity has been abundantly highlighted in previous research (Bijttebier et al., 2012; Corral-Frías et al., 2016; Corral-Frías et al., 2015; Geschwind et al., 2010; Nikolova et al., 2012; Ryba & Hopko, 2012; Vythilingam et al., 2009). These protective effects have also been highlighted in a past ESM study as buffering against the effects of NA reactivity in daily life (Wichers et al., 2007). Results of the current study, although not yet supported by replication, offer interpretation bias as a potential mechanism moderating the effects of the environment on levels of PA. When considering the implications of the past and current findings presented, the need for more research to consolidate and build on these association becomes clear.

The most intriguing finding regarding these analyses was that of the interaction between interpretation bias and positive solitude (choosing to be alone) on levels of PA. Despite the main effect of interpretation bias on the quality of solitude being non-significant, the interaction between interpretation bias and positive solitude on levels of PA highlighted a significant positive effect. This finding suggests that having a more negative interpretation bias and choosing to be alone has a positive and beneficial effect, increasing levels of PA. Interestingly the interaction between interpretation bias and negative solitude on NA also revealed interpretation bias as significantly moderating the association between negative solitude and NA, increasing levels of NA. This suggests that whilst the association between positive solitude and PA was moderated by a negative

interpretation bias to increase PA, the same negative interpretation bias also moderated the association between negative solitude and NA to increase NA. However, this effect was greatest for the interaction with positive solitude on PA. Further analysis of the positive and negative components of interpretation bias highlighted negative interpretation bias as the driving force behind the initial interactions. Whilst positive interpretation bias was found to reduce NA in the presence of negative solitude, it also unexpectedly reduced PA in the presence of positive solitude. However, these effects were buffered against by negative interpretation bias and its positive effect on PA and NA increasing both in the presence of positive and negative solitude respectively. The effects regarding interpretation bias and solitude could suggest that those with a more negative interpretation bias are more sensitive to the quality of their environment in a pattern similar to differential susceptibility. In line with this suggestion, simple slope analysis did reveal significant increases in PA when experiencing positive solitude, and significant increase in NA when experiencing negative solitude in only those with a more negative interpretation bias. However, additional analysis revealed that being alone at the time of the notification significantly moderated the effect of a negative interpretation bias on levels of NA, but not PA. These extra results suggest that the significant interaction between interpretation bias and negative solitude on levels of NA was likely due to having a more negative bias and being alone at the time on the notification, regardless of choice. However, with no confounding effects observed, the unexpected moderating effect of a negative interpretation bias on PA in the context of positive solitude remains.

As yet there has been no previous research examining these specific interaction effects. Despite this, the current findings join a limited number of previous ESM research that have shown similar effects of personality traits (Komulainen et al., 2014) and sensitivity to punishment and reward (Hundt et al., 2013) in daily life on levels of PA and NA. However, of these Komulainen et al. (2014) is the only study to have examined solitude, but only in negative contexts. They demonstrated that both neuroticism and openness significantly moderated the association between experiencing negative solitude and NA, increasing levels of NA. Here, a negative interpretation bias was initially found to moderate the effect of negative solitude on NA in much the same way as neuroticism and openness did in Komulainen et al's (2014) study, although this effect was later found to be confounded. Despite this, the current study represents the first time any moderating effects have been assessed, and found to be significant, regarding the relationship between positive solitude and PA.

It is clear that more research is required to replicate these findings, and further investigate interpretation bias as a potential mechanism by which the effects of the environment on levels of PA are moderated. This is especially true when considering a deficit in PA has been shown to have a significant negative effect on both response to stress, and reward sensitivity (Corral-Frías et al., 2016), and that interpretation bias itself, as discussed above, has been highlighted as a potential causal factor in anxiety vulnerability (Wilson et al., 2006).

3.4.5. Limitations

A significant strength of the current study was the use of ESM to capture repeated measures regarding levels of PA and NA alongside in the moment responses to highly ecologically valid environmental contexts, avoiding retrospective recall bias and mood congruency effects. However, aside from the small sample size and data being based on self-report, there were several other noteworthy limitations.

Firstly, the modified dot-probe task used to measure attention bias was found to be unreliable. This resulted in attention bias being excluded from analysis, meaning that any associations between attention bias and levels of affect in daily life was not possible to assess. This was particularly unfortunate as attention bias represents the most researched cognitive bias and has been shown to predict levels of affect in response to stress (Fox et al., 2010), and moderate the association between mood reactivity and mood recovery in response to negatively induced mood (Clasen et al., 2013). However, the majority of these, and other such studies also measured attention bias using a similar modified dot-probe task, potentially bringing these findings into question. A more reliable measure is required before any definitive conclusions can be made, especially as findings from attention bias modification studies have demonstrated the potential causal effect of an induced attention bias on emotional reactivity (E. Watkins et al., 2008), and mood (Lothmann et al., 2011).

Secondly, although the subjective quality of the participants' environmental contexts was assessed, specific environmental factors were not. For example, whilst the quality of the previous event, current activity and social interactions were assessed, specific information regarding what the events and activities were, to whom they were interacting with and where they were, were not obtained. The inclusion of this information would likely provide a more in depth understanding of

how each cognitive bias impacts on specific environments, activities and events and allow for the assessment of the differential effects of each bias across multiple specific moments in daily life.

Thirdly, the current study did not examine potential biomarkers, such as genetic data, that may have an impact on the development of interpretation bias that was found to influence levels of affect in the course of daily life. A previous ESM study using a monozygotic (MZ) twin design has demonstrated that PA can moderate genetic susceptibility to negative affect reactivity, specifically reducing genetic effects on negative mood throughout the course of daily life (Wichers et al., 2007). The inclusion of genetic data here may have given greater insight into the potential biological mechanism associated with cognitive biases and any genetic overlap with PA and NA. Any genetic associations could assist in targeting those at increased risk of developing negative biases and allow preventions and interventions to be put in place before negative biases are established.

3.4.6. Implications

Despite the limitation of the current study the implications of the findings discussed above are potentially far reaching, although replication efforts will be needed as this was the first time such effects have been assessed. Nevertheless, the current study extends previous research in demonstrating that interpretation bias is an important factor that impacts on level of affect and affective reactivity in daily life. This in turn has important implication for the treatment and intervention of mood and affective disorders. For example, past research has demonstrated that negative affective states are associated with heightened risk of both depression and anxiety (Watson, Clark, & Carey, 1988), and that a negative interpretation bias is often present in those suffering from depression (Lee et al., 2016; Orchard et al., 2016). Interpretation bias may therefore be of particular theoretical and clinical importance for the development of both preventative, and early intervention strategies for those at risk of such disorders. Particularly as research has demonstrated that interpretation bias can be successfully modified to increase positive and decrease negative affective states (Lothmann et al., 2011).

Furthermore, the significant findings regarding the main effects and interaction analyses highlighted interpretation bias as a far more important factor for PA, compared to NA throughout the course of daily life. The negative impact of a negative interpretation bias on PA further

emphasizes the importance and potentially instrumental effects of interpretation bias in regulating PA as well as the protective effects that PA has been shown to have against the effects of stress (Bijttebier et al., 2012; Corral-Frías et al., 2016; Corral-Frías et al., 2015; Geschwind et al., 2010; Nikolova et al., 2012; Ryba & Hopko, 2012; Vythilingam et al., 2009). This, and previous research (Lothmann et al., 2011) and meta-analysis (Menne-Lothmann et al., 2014), regarding the effects of modifying interpretation bias can be seen as implicating interpretation bias as a potential mechanism for the regulation of PA specifically.

Lastly, the result regarding the effect of a negative interpretation bias as moderating the effects of positive solitude to increase PA represented the most intriguing finding of the current study with the most unexpected implications. By showing that a negative interpretation bias can have a positive effect on PA in those choosing to be alone, the current study has revealed for the first time the beneficial effects of choosing to spend time alone on PA for those with more negative but not a more positive interpretation bias. More research is required regarding this effect as, if supported through replication could provide important information for the development and implementation of novel strategies for increasing PA in those with negative interpretation biases.

3.4.7. Conclusion and Future Directions

The current chapter represents the first time the effects of multiple cognitive biases on PA and NA have been assessed using an ESM design, demonstrating both main effects and moderating effects of interpretation bias on levels of affect. Findings have highlighted a consistent association between a more negative interpretation bias and levels of PA specifically, with this association extending to the moderation of multiple environmental effects on levels of PA.

Replication of the findings presented here would further support interpretation bias as an important target not just for treatment, but also preventative interventions aimed at those most at risk, to increase the protective effect of PA and promote resilience against negative mood and affective disorders such as anxiety and depression. However, it is imperative that future research first address the limitations raised in the current study. For instance, if attention bias is to be successfully assessed in terms of the associations examined here, or any other future research, it is essential that a reliable measure is found.

The inclusion of genetic data in future research could also assist in establishing whether there is a heritable, biological mechanism associated with the development of cognitive biases, and whether these potential genetic association overlap with variations in affective states in daily life. If so, findings such as these could provide a way of targeting those at increased risk and provide novel personalised interventions before mood disorder and psychopathology develop. Moreover, the addition of such genetic data, as well as measures of affective disorders such as depression and anxiety would also allow research to assess the efficacy of interpretation bias, and other cognitive biases, as potential intermediate phenotypes for such psychopathologies.

Future ESM research examining such effects should also aim to recruit a larger study sample so that any differential effects between males and females can be examined. This could also include the addition of genetic data to identify variations in biological mechanisms between sexes. If these factors are addressed and effects such as those demonstrated in the current study are confirmed, it could have a significant impact on how the association between interpretation bias and affect is understood, carrying with it, important implications for the development of prevention and intervention strategies.

4. Chapter 4 - The development of cognitive biases: The effect of candidate "sensitivity" variants, and positive and negative life events

4.1. Introduction

The cognitive biases described in previous chapters may be useful intermediate phenotypes for mental health, that are relatively easy to measure, correlate with normal variations in personality traits, and can be linked to emotional resilience and vulnerability (Fox et al., 2009). However, little is known regarding the aetiology of positive or negative cognitive biases and whether, and to what extent, they are influenced by both environmental and genetic factors as well as the interplay between these factors. Drawing on past research and the recently developed CogBIAS hypothesis (Fox & Beevers, 2016), this chapter will explore:

1) The extent to which cognitive biases are influenced by negative *and* positive life events both across time and by-time,
2) The cumulative and independent effect of genetic variants implicated in GxE research of depression and anxiety on cognitive biases both across time and by-time, and,
3) The extent to which the selected candidate variants, both cumulatively and independently moderate the effect of negative *and* positive life events on cognitive biases.

4.1.1. The development of cognitive biases

Whilst decades of research have demonstrated that cognitive biases are important factors in the formation and maintenance of psychopathology, little is known about how such biases develop and the causal mechanisms associated with them. Adolescence represents a period of considerable emotional development, during which time there is a greater risk for developing affective disorders which have been associated with increased levels of emotional reactivity and stress (Powers & Casey, 2015). This increased risk may be in part due to the many social, cognitive, and physiological changes that take place during adolescence. Throughout childhood and adolescence research has demonstrated significant improvements in attentional control, cognitive flexibility, and information processing, with such effects peaking at approximately 15 years of age (Anderson, 2002). A further characteristic of adolescence is represented by changes in environmental processing as susceptibility to social influences increase (Blakemore, 2018). Furthermore, it has been shown that early adolescents (12-14 years of age) are also more socially

influenced by their peers than they are by adults (Knoll et al., 2015), an effect that has not been observed in any other age group, including older adolescents (aged 15 to 18 years).

Beck's original theory of depression suggests that the development of such cognitive processing is purely environmental, with early adversity leading to negative biases that distort how information is received and processed (Beck, 1967). However, Beck and Bredemeier's (2016) unified model of depression considers this relationship from multiple perspectives which included the heritability of such cognitive phenotypes. This is an important factor to consider, as such heritability likely goes some way to explain the differential effects of early adverse environments and could provide a better understanding of why not all those who experience early life adversity develop such skewed cognitive processing.

Several twin studies discussed in detail in Chapter 1 (**Section 1.3.1**) have demonstrated that cognitive biases develop as a result of both genes and the environment (Anokhin et al., 2010; Eley et al., 2007; Eley et al., 2008; Lau & Eley, 2008; Lau et al., 2006; Rijsdijk et al., 2009; Silverman et al., 1999; Stein et al., 1999; Weinberg et al., 2014). Importantly, these studies have focused on both adults and children and demonstrated genetic and environmental effects across several specific cognitive biases. Such findings have highlighted relatively moderate heritability estimates across cognitive biases in attention (42-55% (Rijsdijk et al., 2009)), memory (23-30% (Rijsdijk et al., 2009)) and interpretation bias (24-30% (Eley et al., 2008)), with non-shared environmental effect accounting for a vast majority of the remaining variation. Furthermore, and of great interest, findings from separate twin studies assessing anxiety sensitivity, which has characteristics of both attention and interpretation bias, suggest that the genetic effect on anxiety sensitivity increases from childhood (37% (Eley et al., 2007)) into adulthood (50% (Stein et al., 1999)). In support of this, a further twin study of anxiety sensitivity also demonstrated increasing genetic effects within the same sample with heritability estimates increasing from 35% (Lau et al., 2006) at first measurement, to 44% at a two-year follow-up (Lau & Eley, 2008).

These finding not only suggest that there are heritable components influencing the development of cognitive biases, but also, much like other phenotypes, that these inherited genetic effects increase through life. This supports theoretical perspectives that suggest the aetiology of such cognitive processes are driven by both genetic and environmental factors. However, twin models such as those highlighted above have several limitations, highlighted briefly in chapter

one, including a lack of information regarding which specific environments and genetic variants are at play, and what their relative roles are in the aetiology of cognitive biases. In the following sections the role of environmental factors, such as life events, will be discussed before highlighting research regarding genetic influences and gene-by-environmental interactions specific to cognitive biases.

4.1.2. The effect of life events on cognitive biases

To date, research demonstrating the effect of environmental factors on the development of cognitive biases has tended to focus on attention bias towards threat and interpretation bias regarding emotional faces with a distinct lack of research regarding memory bias. However, much of this research, discussed in detail in chapter 1 (**Section 1.3.2**), has focused on the effects of more severe early life events, such as childhood maltreatment (Fani et al., 2011; Gibb, Schofield, et al., 2009; Pine et al., 2005; Pollak & Kistler, 2002; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003; Rose & Abramson, 1992). Furthermore, the presence of psychopathologies, often found in those exposed to childhood maltreatment, has proved problematic when attempting to infer any causal effect of such severe life events on cognitive biases (Pine et al., 2005). Importantly, studies have also demonstrated consistent associations between such early stressful life events (childhood abuse) in both children and adults without current or previous psychopathologies, on both attention and interpretation biases (Gibb, Schofield, et al., 2009; Pollak & Kistler, 2002; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003). Whilst it may be less surprising that such severe early life events can lead to negative cognitive biases, there is also evidence that more common and milder stressful life events have an influence on the development of cognitive biases such as attention (MacLeod & Hagan, 1992), rumination (Michl et al., 2013), and anxiety sensitivity (Zavos, Wong, et al., 2012). However, only the study by Zavos et al. (2012) has considered this relationship longitudinally, from adolescents to early adulthood, and assessed the possibility of reverse causality by examining whether the stressful life events in question were dependant or independent of an individual's behaviour. This study highlighted the effects of independent stressful life events (i.e., those resulting from external factors and independent of an individual's behaviour), as proximal and less significant than dependant events (i.e., those directly influenced by an individual's behaviour). This suggests that anxiety sensitivity can cause individuals to experience more stressful life events, implicating some degree of reverse causality. However, the effects of

independent life events, did remain significant to some extent implying that such events may still have a part to play in the development of anxiety sensitivity. The result of this study provides important information regarding the occurrence and effects of specific types of stressful life events, as well as the relationship between behaviour and environmental effects on phenotypes such as cognitive biases.

Taken together, the research highlighted above and discussed in detail in chapter 1 suggests the need for further research into the relationship between more common dependant and independent stressful life events and cognitive biases as studies are few and findings are mixed. As previous research thus far has tended to examine single biases, and favour some over others, it is also important to consider such effects across multiple biases simultaneously and assess differential effects of environmental factors. Furthermore, whilst much research to date has focused on negative life events and negative cognitive biases, little is known about the potential associations between positive life events and the development of positive cognitive biases. Lastly, there is still much to be understood regarding the heterogeneity in effect of such life events. For example, genetic variations may account for some of the differential effects of the environment on the development of cognitive biases, as will be discussed next.

4.1.3. Genetic influences on cognitive biases

Whilst the heritability of multiple cognitive biases has been demonstrated through twin studies, molecular genetic research, although still limited, has identified associations between specific candidate variants and cognitive biases. Such research, discussed in detail in chapter 1 (**Section 1.3.4),** has highlighted associations between negative attention and interpretation biases and variations in the much-researched serotonin transporter polymorphism (5-HTTLPR) including the low expression of the A/G SNP rs25531 within the same variant (Fox & Standage, 2012; Pergamin-Hight et al., 2012). Furthermore, research has also provided evidence for associations between negative attention bias and FKBP5 (rs1360780) (Fani et al., 2013), as well as negative rumination and BDNF Val66Met (rs6265) and 5-HTTLPR (Beevers et al., 2009). Whilst these studies focus specifically on associations with negative aspects of cognitive biases, there have also been a handful of studies providing evidence that such association extend to positive aspects of the same cognitive biases. For example, one such study has highlighted that attentional avoidance of negative stimuli and vigilance toward positive stimuli is specific to those homozygotes for the

L allele of 5-HTTLPR (Fox et al., 2009). A further study also found negative attention bias to be associated with COMT Val158Met (rs4680), whilst positive attention bias was found to be associated with DRD2 (rs1800497) (Gong et al., 2013). However, possibly due to publication bias for significant findings, very few non-significant associations between selected candidate variants and cognitive biases have been reported (Gibb, Benas, Grassia, & McGeary, 2009).

However, despite this, these studies are of particular interest, as variants found to be associated with cognitive biases have also been shown to moderate the effects of adverse environments on depression and anxiety across multiple GxE studies highlighted in Chapter 1 (**Section 1.1.3**) (Bukh et al., 2009; Caspi et al., 2003; J Chen et al., 2012; Elovainio et al., 2007; Gunthert et al., 2007; Hosang et al., 2014; Mandelli et al., 2007; Zimmermann et al., 2011). Therefore, such findings suggest shared genetic architecture between cognitive biases and affective disorders such as depression and anxiety. Furthermore, these findings propose that variations within these genetic variants may increase sensitivity to environmental influences.

However, despite studies highlighting significant effects of these candidate variants on cognitive biases, most of them do not take into account the combined effect of all variants. This is particularly important as genetic variants for complex behaviours are unlikely to act in isolation and it therefore may make more sense to consider their combined influence. Furthermore, the effect of environmental factors and how these factors may be moderated by specific genetic variation is also a highly important aspect to consider.

4.1.4. The effects of gene-environment interaction on cognitive biases

The research covered thus far suggests that cognitive biases develop as a result of both genetic and environmental factors. Furthermore, and of particular relevance to the current chapter, it has also been demonstrated that genetic variants said to increase sensitivity to environmental effect on depression and anxiety are the same as those implicated in molecular genetic research of cognitive biases. Although limited, several GxE studies, discussed in detail in Chapter 1 (**Section 1.3.3**), have also shown that the same variants moderate environmental effects on attention bias and, to a lesser extent, memory bias.

The predominant focus of much of this research has been on the moderating effect of 5-HTTLPR on attention bias, in relation to environmental adversities such as childhood physical

abuse (Johnson et al., 2010), stressful life events in children and adolescents (Jenness et al., 2016), and childhood emotional abuse and recent negative life events (Kruijt et al., 2014). However, finding have been inconsistent with variations in the direction of effects between studies (Jenness et al., 2016; Johnson et al., 2010) despite using the same measure of attention bias. Furthermore, the latter of these studies found no significant effect of either 5-HTTLPR or rs25531 in moderating the association between recent negative life events or childhood emotional abuse on attention bias. These conflicting findings further add to the inconsistency regarding the *moderating* effect of 5-HTTLPR on attention bias. Other than attention bias, variations in 5-HTTLPR have also been shown to moderate the effects of recent stressful life events (Canli et al., 2006) and emotional abuse in childhood (Antypa & Van der Does, 2010) on increased levels of rumination, as well as childhood maltreatment on anxiety sensitivity (Stein et al., 2008). However, the latter finding failed to replicate in a large sample with longitudinal measures (Zavos, Wong, et al., 2012).

Other than 5-HTTLPR, research has also provided evidence for COMT Val/Val moderating the effects of stressful life events on attention bias (Jenness et al., 2016) and BDNF Val66Met moderating the effects of childhood stressful life events on memory bias (van Oostrom et al., 2012). However, as most GxE research of cognitive biases has focused on the effects of negative environmental factors on negative biases, little is known about the potential effects of positive environments on positive biases.

Whilst Differential Susceptibility theory (see chapter 1, **Section 1.1.3**) does provide a testable hypothesis through which genetic variants interacting with specific types of environments can lead to affective states, psychopathology or indeed positive and negative cognitive biases, very few studies to date have examined this. However, a study by Fox et al. (2011) has provided evidence for a potential cognitive mechanism, moderated by genetic factors, that results in enhanced environmental sensitivity. Here, carriers of the low-expression form of the 5-HTTLPR (SS, S/Lg or LgLg) developed a stronger negative *and* positive attention bias than those with the high expression form when exposed to an environmental intervention designed to modify attention bias (a CBM procedure in this case). Importantly, this study provided experimental *causal* evidence that a genetic variant can lead to enhanced environmental sensitivity as demonstrated by a stronger attentional bias for a specific category of stimuli (i.e., positive or negative). This study was instrumental for the development of the CogBIAS hypothesis ((Fox & Beevers, 2016) see Chapter 1, **Section 1.3.6**), which suggests that cognitive biases, highlighted here and discussed in

detail in Chapter 1 (**Section 1.2.2**) may represent a potential mechanism through which differential susceptibility occurs.

The reviewed studies illustrate the importance of taking gene-environment interactions into account as an explanation as to why environmental effects, or the isolated effects of genetic variants, vary so much within and across studies of cognitive biases. However, GxE research in relation to cognitive biases remains limited, with a tendency to focus on a single bias such as attention, and to a lesser extent memory, with a distinct lack of research regarding interpretation bias. Furthermore, the study by Fox et al. (2011) remaining one of the only studies to date to assess the effects of both negative *and* positive environments on both a negative *and* positive cognitive bias using in a GxE study. Additionally, this, and the vast majority of GxE research regarding of cognitive biases conducted thus far only assess associations with a single genetic variant. However, many other variants implicated in environmental sensitivity by GxE studies of psychiatric disorders, and importantly their collective effects, are still yet to be assessed in GxE research of cognitive biases.

4.1.5. Aims and hypotheses.

The current study aims to follow-up on the research by Fox et al. (2011) and provide a comprehensive test of the CogBIAS hypothesis (Fox & Beevers, 2016) in a longitudinal framework using data from the CogBIAS-L-S, with a specific focus on the development of cognitive biases. The sample consists of adolescent secondary school students with genetic data and repeated measures of negative and positive life events as well as cognitive biases assessed at 12, 14, and 16 years of age (Booth et al., 2017).

First, the relationship between recent (last 12 months) positively rated and negatively rated life events on cognitive biases in attention, interpretation, and memory will be explored with the hypothesis that negatively rated life events will be associated with more negative and less positive biases, with the opposite effect being observed for positively rated life events. It is expected that these associations will differ in magnitude across all cognitive biases due to separate measures used for each bias. Furthermore, the availability of longitudinal data means it is possible to explore whether life events have a similar effect on cognitive biases over time, or whether these effects increased or decreased across late childhood and into adolescence. Previous twin studies,

mentioned earlier, have shown evidence for the attenuation of environmental influences relative to an increase in genetic effect with older age (Lau & Eley, 2008; Lau et al., 2006). However, given that events are rated as positive or negative by the participants themselves, it is possible that these associations are simply the result of their increased positive or negative interpretation of each of the life events (i.e., their existing biases). In order to explore this possibility, a sensitivity analyses will be conducted excluding any events in which the positive or negative rating could be influenced by cognitive biases. It is hypothesised that associations between these corrected life events and cognitive biases will remain significant in these analyses, suggesting that they are not simply the result of differences in the interpretation of the events. It is also possible that any association between life events and cognitive biases are the result of reverse causality, with cognitive biases influencing life events. In order to explore this possibility, a further sensitivity analyses will be conducted excluding any dependent events that could have been the result of the participants behaviour. It is hypothesised that associations between life events and cognitive biases will remain significant in these analyses providing support for a causal role of life events on cognitive biases.

Next, genetic variants previously implicated to increase sensitivity to environmental effects in GxE studies of depression and anxiety, will be systematically selected and tested for their associations with cognitive biases in attention, interpretation, and memory. In contrast to previous studies, a candidate gene polygenic approach will be applied in primary analysis to assess the cumulative effect of all selected sensitivity variants in a candidate sensitivity score (CSS), before secondary analysis is conducted assessing the individual effect of each candidate variant independently. This approach will provide a better understanding of how these variants effect different positive and negative cognitive biases on an additive level and give insight into their cumulative effect as these variants are unlikely to act alone and are subject to the effect of other variants.

It is hypothesised that there will be an association between the systematically selected candidate sensitivity variants and cognitive biases. Specifically, it is expected that the main effect of the CSS will have a significant effect on both negative *and* positive biases in attention, interpretation and memory. However, these effects will likely differ for the individual candidate sensitivity variants when investigated in isolation. Similar to the assessment of life events, this study also aims to assess whether the selected candidate sensitivity variants have consistent effects

on cognitive biases over time. Given the relatively short time period of the study, it is hypothesised that the effects of both the CSS and each individual variant will not change significantly across time.

Following this, the study will explore the interaction between the candidate sensitivity variants and positive and negative life events in the prediction of cognitive biases in attention, interpretation, and memory. As with the previous approaches, the effect of the CSS will be assessed before the individual effect of each candidate sensitivity variants are assessed individually. It is hypothesised that the association between life events and cognitive biases will be significantly moderated by the CSS. Specifically, the number of positive and negative life events will have a greater impact on both positive and negative cognitive biases in those with a higher CSS. Similarly, when assessing each candidate sensitivity variants individually, the number of positive and negative life events will have a greater impact on both positive and negative cognitive biases in those with two copies of the sensitivity allele. The assessment of both positive and negative life events will also allow for the study to assess whether interactions between the select candidate sensitivity variants and life events lead to negative or enhancing biases over the three timepoints, and also whether they operate in a "for better or worse" manner, in line with the Differential Susceptibility hypothesis.

Finally, in order to ensure that any gene-environment interaction effects are not confounded by gene-environment correlation, the relationship between the candidate sensitivity variants and negative and positive life events will also be tested. All significant gene-environment interactions will also be subject to sensitivity analysis with regards to the two specific sets of life events. Sensitivity analysis will also be conducted to examine the effects of psychopathologies depression and anxiety across all significant results.

4.2. Methods

4.2.1. Sample

The current study used pre-existing data collected as part of the CogBIAS-L-S. The sample consisted of 504 11-12-year-olds (226 males, 278 females) at the first wave of data collection (Wave 1). However, this was reduced to 501 (224 males and 277 females) as a result of missing cognitive biases data. Furthermore, due to a drop in the retention rate at subsequent waves of data collection this number was reduced further to 448 participants at 14 years of age (198 males and 250 females) by Wave 2, and to 410 at 16 years of age (169 males and 241 females) by Wave 3.

Quality control and population stratification of the genetic data resulted in a reduced sample of 391 (191 males and 200 females) at Wave 1, 349 (167 males and 182 females) at Wave 2, and 323 (146 males and 177 females) at Wave 3. This reduced sample was used for all analysis that included genetic data. Further detail regarding the sample, recruitment process and inclusion criteria please can be found in Chapter 2 (**Section 2.2.2**).

4.2.2. Procedure

Participants were assessed for cognitive biases, life experiences, and depression and anxiety in small groups and across two separate test sessions with the majority of these sessions taking place at their respective schools. However, in some cases test sessions were conducted at the Department of Experimental Psychology, University of Oxford. For more information regarding these procedures please see Chapter 2 (**Section 2.2.3**) and the article, *"The CogBIAS longitudinal study protocol. Cognitive and genetic factors influencing psychological functioning in adolescence"* (Booth et al., 2017).

4.2.3. Measures

Cognitive biases in attention were assessed using a pictorial *dot probe task* consisting of both angry and happy faces. Interpretation bias of hypothetical positive and negative social and non-social scenarios were assessed using *The Adolescent Interpretation and Belief Questionnaire* (AIBQ). Memory bias was measured using *The Self-Referential Encoding Task* (SRET), assessing both endorsed and recalled positive and negative words. Exposure to life events was assessed using *The Child Adolescent Survey of Experiences – Child version* (CASE–C) with childhood mental health specific to depression and anxiety measured using the *Revised Children's Anxiety and*

Depression Scale - Short Form (RCADS-SF). Cognitive bias measures assessed in the current chapter consist of both positive and negative scores that were used to calculate an overall bias score. Interpretation bias was also assessed in terms of social and non-social interpretations with positive and negative components for each. Both the overall bias scores, and the separate positive and negative bias components were analysed separately throughout the current study. Detailed information regarding these measures is provided in Chapter 2 (**Section 2.2.4**).

4.2.4. Genotyping

Saliva samples were collected from all participants using *DNA Genotek Oragene OG-500* collection kits. Following DNA extraction all samples were genotyped using the Illumina Human Omni express-24 chip. Separate genotyping was conducted through PCR to capture the serotonin transporter polymorphism (5-HTTLPR) with further restriction enzyme digest to capture the 5-HTTLPR SNP rs25531. Imputation was also conducted using the 1,000 genome reference panel to include variants that were not captured by the Illumina Human Omni express-24 chip. More information regarding the genotyping and imputation can be found in Chapter 2 (**Section 2.2.5**).

4.2.5. Candidate Gene Selection

All selected genetic variance had been previously implicated to increase sensitivity to environmental effect in GxE studies of symptoms and traits related to depression and anxiety, or depression and anxiety directly. A systematic Pubmed search, detailed in Chapter 2, identified 28 candidate variants across 15 studies (see **Table 4.1**). As the selected genetic variance had been implicated by GxE research to increase sensitivity to environmental effects, the current thesis will refer to the selected variants as "candidate sensitivity variants" throughout the current chapter.

Table 4.1. The list of candidate genes and variants included in the study based on the systematic PubMed search.

Gene	Variant	Sensitivity Allele	Previous Research	GxE findings	In CSS
FAAH	rs324420	A	(Lazary et al., 2016)	Moderated chronic childhood adversity on depression and anxiety	YES
NGF	rs6330	T	(Hudson et al., 2013)	Moderated response to psychological treatments for Anxiety	YES
OXTR	rs53576	C	(Chang et al., 2014)	Moderated Oxytocin/dopamine interaction and neuroticism traits	YES
GSK3B	rs6782799	C	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
NR3C2	rs5522	Val (G)	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
HTR1A	rs878567	C	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
FKBP5	rs3800373	G	(Scheuer et al., 2016)	Moderated adverse life events on depression and anxiety risk	YES
FKBP5	rs1360780	T	(Scheuer et al., 2016)	Moderated adverse life events on depression and anxiety risk	NO
FKBP5	rs4713916	A	(Scheuer et al., 2016)	Moderated adverse life events on depression and anxiety risk	NO
CNR1	rs7766029	T	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
CNR1	rs1049353	G	(Agrawal et al., 2012)	Moderated childhood physical abuse on anhedonic depression	NO
OPRM1	rs1799971	A	(Slavich et al., 2014)	Moderated socially unpleasant life events on depression	YES
NPSR1	rs324981	T	(Klauke et al., 2014)	Moderated life events on anxiety sensitivity	YES
BDNF	rs6265	Met (T)	(van Winkel et al., 2014)	Moderated social stress on depression symptoms	YES
DRD2	rs1800497	T	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
HTR3A	rs1062613	T	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
TPH1	rs1800532	T	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
TPH2	rs4570625	T	(Forssman et al., 2014)	Moderated early life stress on heightened attention to social fear	YES
HTR2A	rs6314	A	-	-	NO
HTR2A	rs6313	T	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
HTR2A	rs6311	A	-	-	NO
SLC6A2	rs2242446	C	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
SLC6A2	rs5569	A	(Bousman et al., 2017)	Moderated childhood abuse on adult depressive symptom severity	YES
SLC6A4	5HTTLPR	S	(Caspi et al., 2003)	Moderated life events and childhood maltreatment on depression	YES
SLC6A4	rs25531	G	-	-	YES
CRHR1	rs110402	A	(Keers & Pluess, 2017)	Moderated childhood life quality on adult environmental sensitivity	YES
CHRNA4	rs1044396	T	(Grazioplene et al., 2013)	Moderated childhood maltreatment on personality/developmental sensitivity	YES
COMT	rs4680	Val (G)	(Baumann et al., 2013)	Moderated early life experiences on Anxiety sensitivity	YES

Note: Two variants (rs6314 and rs6311) were also included due to being in high linkage disequilibrium (LD) with rs6313 which was selected as a result of the systematic PubMed search. The last column of the table also indicates whether a variant was included in the candidate sensitivity score. Variants in LD with other variants in the same gene were randomly removed from the candidate sensitivity score to prevent type I error.

4.2.6. Statistical Analysis.

First, the relationship between each of the cognitive biases, within and across each time point, were tested using Pearson's correlations. This allowed for the stability of each of the measures to be assessed across each wave of data collection. This was also conducted for the each of the positive and negative bias components.

Following this, using the full sample of 501 individuals, linear mixture models were constructed for each of the biases using data from each timepoint with random intercepts to account for the autocorrelation of data from the same individual over time. The fixed effects of time were added to these models to assess whether the cognitive biases changed significantly across time. Next, the random slopes of time were included, and likelihood ratio tests used to indicate whether the inclusion of these random effects improved model fit.

In order to test the relationship between life events and cognitive biases across the three time points, the life event score (number of life events reported) was included in the above linear mixture models as a time-varying fixed effect across the full sample. Separate models were fit for each of the cognitive biases and positive and negative life event scores. Next, life event-by-time interactions were included in the above models to assess whether the relationship between life events and cognitive biases varied over time. Sensitivity analysis was then conducted using the two specific sets of life events derived from the original CASE inventory. In the first set any events in which the positive or negative rating were found to be influenced by pre-existing cognitive biases were excluded, whilst the second set further excluded any life events that were ambiguous or dependent on an individual's behaviour. Sensitivity analysis was conducted separately for each of each set of life events.

Two approaches were applied in order to test the relationship between the candidate sensitivity variants and cognitive biases in a reduced sample of 391 individuals of European decent. In the primary analysis, the additive effect of all candidate sensitivity variants was summed up to create the CSS, including 23 of the 28 variants as five variants were in high linkage disequilibrium (LD) with other variants and were therefore randomly removed to prevent type I error (false positive) as described in **Table 4.1**. This was included as a fixed effect in separate linear mixture models for each of the cognitive biases. In the secondary analysis, candidate sensitivity variants were tested one at a time in separate models for each of the cognitive biases.

Next, primary analysis regarding CSS-by-time and secondary analysis regarding each individual candidate sensitivity variant-by-time interaction were included in the above models to assess whether the relationship between the selected candidate sensitivity variants and cognitive biases varied over time.

Following this, in order to test whether the candidate sensitivity variants moderated the effects of life events on cognitive biases, models were constructed that included the main effects of life events, candidate sensitivity variants and candidate sensitivity variants-by-life event interactions. Separate models were fit for each of the cognitive biases and positive and negative life event scores. Initially, as primary analysis, the CSS was included as the genetic factor in these models. However, candidate sensitivity variants were also tested one at a time in separate models by way of secondary analysis. Age and gender were included as fixed effect covariates across all analysis. All analyses were conducted using STATA 12.1 (StataCorp, 2011).

Finally, sensitivity analysis was conducted across all significant primary and secondary GxE finding using the two specific sets of life events discussed earlier. Furthermore, to ensure that any initially significant GxE findings were not confounded by a pre-existing association, correlations between the CSS and both negative and positive life events were assessed. This was also performed across each candidate sensitivity variant individually. Further sensitivity analysis was also conducted to assess the effect of psychopathology across all significant findings.

4.3. Results

4.3.1. Descriptive statistics

The relationship between the cognitive biases, both within and across time, were tested using Pearson's correlation. This also provided information on the stability of the measures over the course of the study. The results are presented in the correlation matrix in **Table 4.2** and **Table 4.3.** Social and non-social interpretation bias and memory bias scores were significantly correlated across the three time points, respectfully (r=0.423-0.549, r=0.453-0.515, r=0.414-0.484), indicating stability of these measures (**Table 4.2**). Findings were similar when exploring the positive and negative components of each bias (**Table 4.3**) which also demonstrated significant within measure correlations between time points (negative social interpretation, r=0.372-0.594; positive social interpretation, r=0.303-0.385; negative non-social interpretation, r=0.422-0.462; positive non-social interpretation, r=0.471-0.377; positive memory, r=0.424-0.470; negative memory, r=0.329-0.492). Correlations between these bias components were smaller, but significant both within, (cognitive biases, wave 1: r=0.341-0.496; positive and negative component, wave 1: r=-0.265-0.594), and across (cognitive biases, r=0.268-0.638; positive and negative component, r=-0.329-0.634) waves.

However, there was a distinct lack of correlation between waves regarding attention bias (happy bias and angry bias: (r=-0.043-0.72, r=0.006-0.120)) with both also not showing any correlation with the other biases either within, (r=-0.28-0.002, r=-0.036-0.036) or across (r=-0.052-0.076, r=-0.036-0.96) waves.

Table 4.2. Correlation matrices displaying the correlation of each of the cognitive biases both within and between wave 1 (W1), wave 2 (W2), and wave 3 (W3).

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Angry bias W1	1														
2	Happy bias W1	-.043	1													
3	Social Int. bias W1	.036	.002	1												
4	Non-social Int. bias W1	-.036	-.028	**.463*****	1											
5	Memory bias W1	.038	-.024	**.496*****	**.341*****	1										
6	Angry bias W2	.006	-.057	-.022	.093	.015	1									
7	Happy bias W2	.072	.028	-.038	-.042	-.098	.010	1								
8	Social Int. bias W2	.096	-.052	**.549*****	**.303*****	**.383*****	-.036	-.019	1							
9	Non-social Int. bias W2	-.004	.001	**.379*****	**.515*****	**.394*****	.054	-.043	**.510*****	1						
10	Memory bias W2	.038	.042	**.360*****	**.282*****	**.484*****	.055	.006	**.570*****	**.430*****	1					
11	Angry bias W3	**.120***	.015	-.008	-.003	**.136***	-.012	.018	-.006	-.016	-.002	1				
12	Happy bias W3	-.012	-.015	**-.110***	-.052	-.055	.018	-.046	-.085	-.061	-.065	.030	1			
13	Social Int. bias W3	.083	-.033	**.423*****	**.303*****	**.341*****	.015	-.009	**.638*****	**.489*****	**.491*****	-.083	-.044	1		
14	Non-social Int. bias W3	.016	.076	**.366*****	**.453*****	**.268*****	.078	-.059	**.386*****	**.562*****	**.348*****	-.025	-.080	**.513*****	1	
15	Memory bias W3	.047	.004	**.297*****	**.311*****	**.414*****	.040	-.059	**.395*****	**.366*****	**.561*****	.002	.001	**.542*****	**.428*****	1

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

Table 4.3. Correlation matrices displaying the correlation of each positive and negative components within and between wave 1 (W1), wave 2 (W2), and wave 3 (W3).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	1																	
2	**-.215*****	1																
3	**.517*****	.041	1															
4	**-.112***	**.385*****	**-.142****	1														
5	**-.212*****	**.262*****	**-.124***	**.181*****	1													
6	**.418*****	**-.265*****	**.227*****	**-.244*****	**-.265*****	1												
7	**.594*****	**-.186*****	**.286*****	-.104*	**-.176*****	**.324*****	1											
8	**-.119***	**.385*****	.0350	**.278*****	**.139****	**-.178*****	**-.235*****	1										
9	**.420*****	-.102	**.462*****	-.093	**-.166****	**.310*****	**.609*****	-.021	1									
10	-.092	**.200*****	-.0795	**.471*****	**.186*****	**-.226*****	-.0467	**.449*****	-.065	1								
11	**-.198*****	**.189*****	-.0713	**.186*****	**.470*****	**-.185*****	**-.329*****	**.360*****	**-.141****	**.255*****	1							
12	**.306*****	**-.167****	**.195*****	**-.182*****	**-.178*****	**.492*****	**.463*****	**-.269*****	**.353*****	**-.249*****	**-.272*****	1						
13	**.372*****	**-.204*****	**.237*****	**-.150****	**-.187*****	**.240*****	**.634*****	**-.228*****	**.499*****	-.0875	**-.305*****	**.379*****	1					
14	-.072	**.303*****	-.0143	**.240*****	**.184*****	**-.154****	**-.129***	**.437*****	-.101	**.332*****	**.232*****	**-.239*****	**-.153****	1				
15	**.317*****	**-.168****	**.422*****	-.068	**-.181*****	**.224*****	**.413*****	-.102	**.577*****	-.041	**-.200*****	**.286*****	**.613*****	-.061	1			
16	-.084	**.163****	-.096	**.377*****	**.183*****	**-.072**	**-.068**	**.211*****	-.069	**.464*****	**.186*****	**-.127***	.010	**.411*****	-.047	1		
17	**-.118***	**.185*****	-.092	**.202*****	**.424*****	**-.152****	**-.189*****	**.216*****	**-.137****	**.208*****	**.524*****	**-.189*****	**-.272*****	**.252*****	**-.204*****	**.275*****	1	
18	**.229*****	**-.183*****	**.207*****	**-.174*****	**-.205*****	**.329*****	**.384*****	**-.149****	**.306*****	**-.174*****	**-.225*****	**.529*****	**.483*****	**-.257*****	**.335*****	**-.165****	**-.298*****	1

1	Negative social interpretation bias	**7**	Negative social interpretation bias	**13**	Negative social interpretation bias
2	Positive social interpretation bias	**8**	Positive social interpretation bias	**14**	Positive social interpretation bias
3	Negative non-social interpretation bias	**9**	Negative non-social interpretation bias	**15**	Negative non-social interpretation bias
4	Positive non-social interpretation bias	**10**	Positive non-social interpretation bias	**16**	Positive non-social interpretation bias
5	Positive memory bias	**11**	Positive memory bias	**17**	Positive memory bias
6	Negative memory bias	**12**	Negative memory bias	**18**	Negative memory bias

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

4.3.2. The effects of time on cognitive biases

Mixture models were constructed for each of the biases using data from each timepoint with random intercepts to account for the autocorrelation of data from the same individual over time. A likelihood ratio test suggested that this model provided a better fit for the data for social and non-social interpretation bias, and memory bias than a standard linear regression. However, for attention bias (angry bias and happy bias) model fit was substantially worse than a standard linear regression. This is explained by the very low correlation between the measures of attention bias across time, which were all less than 0.13 and only significant for angry bias at wave 1 and wave 3 (see **Table 4.2**). Reliability analysis suggested that the instability of this measure was likely the result of a lack of reliability of the dot probe task which showed a split half reliability of -0.02 at wave 1, 0.10 at wave 2, and 0.27 at wave 3 for angry bias (response to angry facial expressions). Happy bias (response to happy facial expressions) also demonstrated a poor split half reliability of 0.08 at wave 1, 0.18 at wave 2 and 0.22 at wave 3. Due to this low reliability, attention bias was dropped from all downstream analysis.

Next, the fixed effects of time were included in the models to assess whether the cognitive biases changed significantly over time. Results from these analyses suggested an increase in negative memory bias (β=0.23, 95%CI=0.18-0.28, p=<0.000) and a small decrease in positive biases for social (β=-0.06, 95%CI=-0.10--0.01, p=0.012) and non-social interpretation (β=-0.08, 95%CI=-0.13--0.03, p=0.001) over the course of the study. Finally, the random effects of time (random slopes) were included, and likelihood ratio tests used to indicate whether the inclusion of these random effects improved model fit. Model fit was improved for each of the biases suggesting that the effects of time on cognitive biases varied significantly between individuals.

4.3.3. Life Events and Cognitive Biases.

Descriptive statistics of the CASE

The number and percentage of individuals endorsing each item of the CASE questionnaire for the assessment of life events across each of the three timepoints are presented in the **appendix (i)**. The most frequently endorsed items were "I stayed away from home overnight", and "I did well in an important test or exam", with endorsements ranging from 357-408 and 315-388 across the three timepoints respectively. Conversely, the least frequently endorsed items were "I found out I had to repeat a grade in school", and "Someone broke into my house" with endorsements ranging from 3-10 and 15-23 respectively across the three timepoints. The majority of items showed little variability in terms of their subjective rating within or across time. For example, the item "Someone in my family was really sick or injured" was rated as negative by 98.1%, 97.7%, and 98.4% of those who endorsed the item at wave one, two and three respectively. Other items were consistently rated as positive events, including the item "I (or my team) won a prize, award or contest" which was rated as positive by 99.7%, 99.3%, and 100% of those who endorsed the items at wave one, two and three, respectively. A small number of items showed considerable variability in terms of subjective rating of negativity or positivity. For example, the item "My parent(s) stayed away from home overnight" was only rated as negative by 40%, 36.2%, and 30.8% at wave 1, 2, and 3, respectively, by those who reported experiencing it.

Effects of life events on cognitive biases

The effects of the number of negative and positive life events on cognitive biases across the three waves were tested by including positive and negative life event scores as fixed effects in the models described above in **Section 4.3.2**. Separate models were tested for each of the biases and the positive and negative components of each bias. The results of these analyses can be found in **Table 4.3** and **Table 4.4** respectively.

Table 4.4. Results of linear mixture models exploring the effects of negative and positive life events on cognitive biases

	Negative life event score			Positive life event score		
	β	95% CI	P	β	95% CI	P
Memory bias	.15	(.09-.20)	**$2.50x10^{-8}$* ($7.50 x10^{-8}$)****	-.07	(-.12--.02)	**.008* (0.011)****
Non-social interpretation bias	.11	(.06-.17)	**$1.91x10^{-5}$* ($2.87x10^{-5}$)****	-.04	(-.09-.01)	.140
Social interpretation bias	.09	(.04-.14)	**.001* (.001)****	-.08	(-.12--.03)	**.003* (.007)****

Note: Displayed are the beta values, 95% confidence intervals and p-values for the effects of both positive and negative life event score across time for cognitive biases. Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

The number of negative life events reported had a significant positive association with all three of the cognitive biases, with the greatest associations observed for memory bias (see **Table 4.4**). Furthermore, all associations also remained significant following correction for multiple testing. The results indicate that individuals who reported more negative life events had stronger negative memory, social and non-social interpretation biases. The association between negative life events and cognitive biases were further explored by considering the positive and negative components of each bias separately (see **Table 4.5**). In these analyses, negative life events were not significantly associated with the positive components of the biases. However, they were significantly associated with the negative components of the biases. Specifically, individuals who reported more negative life events endorsed and recalled more negative words in the SRET task (*negative memory bias*) and provided more negative interpretations of social and non-social situations (*negative social and non-social interpretation bias*) across the three waves.

No significant association was observed between the number of positive life events reported and non-social interpretation biases. However, positive life events were significantly associated with both memory and social interpretation bias and remained so following correction for multiple testing (see **Table 4.4**). Positive life events were negatively associated with both biases. That is, those who reported a high number of positive life events had stronger positive memory and social interpretation bias across the three timepoints. When assessing the positive and negative components of the biases, findings were only significant for the positive components of

memory bias and, to a lesser extent, social interpretation bias. Specifically, individuals who reported more positive life events, endorsed and recalled more positive words in the SRET and provided more positive social interpretations in the interpretation bias questionnaire across the three timepoints (see **Table 4.5**).

Table 4.5. Results of linear mixture models exploring the effects of negative and positive life events on positive and negative components of the cognitive biases

	Negative life event score			Positive life event score		
	β	95% CI	P	β	95% CI	P
Positive memory bias	-.02	(-.07-.03)	.473	.12	(.07-.17)	**6.55×10^{-6}* (3.93×10^{-5})****
Negative memory bias	.20	(.15-.25)	**2.22×10^{-16}* (1.33×10^{-15})****	-.01	(-.06-.04)	.725
Negative Non-social interpretation bias	.11	(.06-.17)	**1.96×10^{-5}* (3.92×10^{-5})****	-.02	(-.07-.03)	.441
Negative Social interpretation bias	.13	(.08-.18)	**3.06×10^{-7}* (9.18×10^{-7})****	-.05	(-.09-.00)	.060
Positive Non-social interpretation bias	-.05	(-.11-.00)	.061	.04	(-.01-.09)	.146
Positive Social interpretation bias	.02	(-.04-.07)	.506	.10	(.04-.15)	**3.74×10^{-4}* (.001)****

Note: Displayed are the beta values, 95% confidence intervals and p-values for the effects of both positive and negative life events across time for the positive and negative bias components. Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

Life event-by-time interactions on cognitive biases

In order to test whether the effects of negative or positive life events were similar across the three timepoints, life-event-by-time interactions were included in the above models. These results are presented in **Table 4.6**. None of the interactions were significant, suggesting that the effects of negative and positive life events were similar across timepoints.

Table 4.6. Results of linear mixture models exploring the interaction between negative and positive life events and time on cognitive biases

Cognitive bias	Negative life event-by-time			Positive life event-by-time		
	β	95% CI	P	β	95% CI	P
Memory bias	.04	(-.02-.09)	.164	.02	(-.03-.08)	.423
Non-social Interpretation bias	.04	(-.02-.09)	.192	.01	(-.04-.07)	.664
Social Interpretation bias	.02	(-.04-.07)	.546	.01	(-.04-.06)	.703

Note: The table above shows the beta values, confidence intervals and p-values for the effects of both positive life events by time and negative life events by time interactions across the cognitive biases. Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

Findings were similar when conducting analyses separately on the positive and negative components of the biases (see **Table 4.7**). However, there was a significant negative life event-by-time interaction for the negative component of memory bias (*negative memory bias*). Here, the positive association suggests that those who had experienced more negative life events endorsed and recalled more negative words with the strength of this relationship also shown to increase over time. Wave 1 saw the smallest effects of negative life events (β=0.15, 95%CI=0.08-0.22, p=1.95x10^{-5}), whilst at wave 2 this effect was seen to dramatically increase (β=0.33, 95%CI=0.25-0.41, p=8.65x10^{-15}). However, whilst still remaining significant, both effect size and significance was found to decrease by wave 3 (β=0.32, 95%CI=0.21-0.44, p=6.60x10^{-8}).

Table 4.7. Results of linear mixture models exploring the interaction between negative and positive life events and time on negative and positive components of cognitive biases.

Cognitive bias components	Negative life event-by-time			Positive life event-by-time		
	β	95% CI	P	β	95% CI	P
Positive memory bias	-.01	(-.07-.05)	.744	-.05	(-.10-0.01)	.122
Negative memory bias	.08	(.02-.14)	**.007* (.042)****	<.01	(-.06-0.06)	.928
Negative non-social Interpretation bias	.02	(-.03-.08)	.394	-.02	(-.07-0.04)	.528
Negative social Interpretation bias	.02	(-.03-.08)	.382	-.01	(-.07-0.04)	.632
Positive non-social Interpretation bias	-.03	(-.09-.03)	.318	-.04	(-.10-0.01)	.133
Positive Social Interpretation bias	<.01	(-.06-.06)	.951	-.04	(-.10-0.02)	.212

Note: The table above shows the beta values, confidence intervals and p-values for the effects of both positive life events by time and negative life events by time interactions across the positive and negative bias components. Results marked with a single asterisk '*' represents a nominally significant result, and those marked with a double asterisk '**' represents a result significant following multiple testing correction.

4.3.3.1. Sensitivity analyses: Reporting biases

The CASE questionnaire requires that participants endorse items that they had experienced, and also provide a subjective rating of how negative or positive the endorsed event was. Descriptive statistics provided in **appendix (i)** suggested that there was considerable variation in the subjective ratings of several events. That is, the same events may be counted as positive for some individuals, and negative for others. This means that the relationship between the number of negative events endorsed, and negative cognitive biases may simply be the result of a reporting bias. This may occur if individuals with negative cognitive biases, despite experiencing similar numbers of events as those with positive cognitive biases, rate more of these life events as negative. In order to explore this possibility, the effects of cognitive biases on the ratings of each item in the CASE questionnaire was investigated using a logistic regression. The findings from these analyses

are presented in **appendix (ii)**. Of the 38 items, the subjective ratings of 19 of the items were significantly associated with one or more of the three cognitive biases. For example, those with a more negative memory, social or non-social interpretation bias were significantly more likely to rate the item "my parent(s) stayed away from home overnight" as negative when compared with those with positive biases.

Effects of life events on cognitive biases using the reduced 19-item CASE

In order to test whether the potential reporting biases were responsible for the significant associations reported in **Section 4.3.3**, analyses exploring the association between life events and cognitive biases were rerun using a reduced version of the CASE that excluded the 19 items for which subjective ratings were associated with cognitive biases. In order to limit multiple testing, the sensitivity analyses only included findings that were significant in the original analyses.

The effects of the 19-item reduced list regarding negative life events on cognitive biases were in the same direction to those from the full CASE list. However, the effect sizes were smaller and only one previously significant finding, for memory bias, remained significant (β=0.06, 95%CI=0.00-0.11, p=0.042, FDR=0.125), albeit to a nominal level. Analyses of the reduced list of negative life events and the positive and negative bias components also revealed similar results to those using the full CASE list. Specifically, as with the full CASE list, the occurrence of negative life events was not associated with any of the positive components of cognitive biases. However, replicating results from the full CASE list, they were significantly and positively associated, following multiple testing corrections, with the negative component of memory bias (*negative memory bias*: β=0.13, 95%CI=0.07-0.18, $p=6.24\text{x}10^{-6}$, FDR=$3.74\text{x}10^{-5}$), as well as the negative component of social interpretation bias (*negative social interpretation bias*: β=0.07, 95%CI=0.02-0.13, p=0.007, FDR=0.022). The original significant result regarding the negative component of non-social interpretation bias (*negative non-social interpretation bias*) was no longer significant when using the reduced 19-item CASE list (β=0.04, 95%CI=-0.02-0.10, p=0.164), suggesting that the original result may have been driven by a bias in reporting.

The effects of the 19-item reduced list regarding positive life events on cognitive biases were also in the same direction to those from the full CASE list, and with similar effect sizes. Specifically, positive life events remained negatively associated with both memory bias (β=-0.09,

95%CI=-0.15--0.04, *p*=0.001, FDR=0.004) and social interpretation bias (β=-0.08, 95%CI=-0.13--0.02, *p*=0.008, FDR=0.011) following multiple testing corrections, suggesting that individuals who reported more positive life events had a more positive memory and social interpretation bias, when accounting for reporting bias.

Analyses regarding the effects of positive life events on the positive and negative components of the biases also revealed similar results for the reduced 19-item CASE list as it did for the full version. That is, positive life events were not associated with any of the negative components of cognitive biases but were significantly associated with the positive components. Specifically, as with the analysis of the full CASE list, experiencing more positive life events was associated with increases in the positive component of memory bias (*positive memory bias*: β=0.08, 95%CI=0.02-0.14, *p*=0.007, FDR=0.039) and the positive component of social interpretation bias (*positive social interpretation*: β=0.07, 95%CI=0.01-0.13, *p*=0.017, FDR=0.051). However, only the association with the positive memory bias component survived correction for multiple testing.

The only significant life event-by-time interaction identified using the full CASE was the interaction between negative life events and time on the negative component of memory bias (*negative memory bias*) (see **Table 4.7**). This interaction remained significant when using the 19-item CASE list, albeit at a nominal level (β=0.07, 95%CI=0.00-0.13, *p*=0.042, FDR=0.215).

4.3.3.2. Sensitivity analyses: Independent life events

It is also possible that the associations between life events and cognitive biases are the result of reverse causality, with cognitive biases influencing life events. In order to explore this possibility, further sensitivity analysis was conducted focusing on events that were unlikely to be dependent on the participants behaviour in line with past research (J. L. Allen & Rapee, 2009). Any item on the reduced 19-item list that had been identified as dependent or ambiguous (J. L. Allen & Rapee, 2009) were removed leaving a further reduced list of 11 'independent' items (see **Table 4.8**). Results regarding sensitivity analysis using the reduced 11-item independent CASE list are detailed below. Again, in order to limit multiple testing, only findings that were significant using the full CASE item list were reassessed.

Table 4.8. Displaying the reduced 19-item CASE list and the 11-item independent CASE list.

Reduced item CASE Subset Lists	
19-Item CASE Subset	11-Item Independent CASE Subset
We moved house	We moved house
Someone special to me moved away (not in family)	Someone special to me moved away (not in family)
Someone in my family was really sick or injured	Someone in my family was really sick or injured
My parent(s) had a baby/found out they are going to have a baby	My parent(s) had a baby/found out they are going to have a baby
I was teased or bullied	-
I was really sick or injured	-
I did well in an important test or exam	-
My parent(s) lost their job	My parent(s) lost their job
I broke up with my boyfriend or girlfriend	-
I saw something bad happen	I saw something bad happen
Someone in the family died	Someone in the family died
My mum got married, engaged or began seeing someone else	My mum got married, engaged or began seeing someone else
Someone broke into my house	Someone broke into my house
I was chosen to be a class monitor, prefect or school captain	-
I was seriously told of or punished by a teacher	-
I took up a new hobby/sport/activity	-
I found out I had to repeat a grade in school	-
Someone special to me was really sick or injured (not in family)	Someone special to me was really sick or injured (not in family)
My dad got married, engaged or began seeing someone else	My dad got married, engaged or began seeing someone else

Effects of life events on cognitive biases using the reduced 11-item CASE of independent events

Analysis of the negative life events from the reduced 11-item independent CASE list revealed no significant findings across all three cognitive biases. However, the independent negative life events did remain significantly associated with the negative social interpretation bias component (*negative social interpretation bias*: β=0.06, 95%CI=0.01-0.11, p=0.027, FDR=0.060), and the negative memory bias component (*negative memory bias*: β=0.07, 95%CI=0.02-0.12, p=0.007, FDR=0.044). Although only the latter survived correction for multiple testing. The number of positive life events from the reduced 11-item independent CASE list was not significantly associated with any of the previously significant cognitive biases or their

positive and negative components. The only significant life event-by-time interaction identified using the full CASE was the interaction between time and negative life events on the negative component of memory bias (*negative memory bias*) (see **Table 4.7**). This interaction remained significant when using the 11-item CASE list, albeit at a nominal level (*negative memory bias*: β=0.08, 95%CI=0.01-0.14, *p*=0.019, FDR=0.113).

4.3.4. Genetic sensitivity variants and cognitive biases.

Descriptive statistics

Genotypic data regarding 391 individuals within the CogBIAS-L-S sample was assessed for Hardy Weinberg equilibrium (HWE) and minor allele frequencies (MAF) across all of the 28 candidate variants selected (see **Table 4.9**). All minor allele frequencies (MAF) were in keeping with previous research, and there was no substantial deviation from HWE. Whilst there were five variants (rs6330, rs1800532, rs6311, rs6313, rs2242446) that did show nominally significant p-values, these were not significant following correction for multiple testing (all Q values > 0.1).

The coding for each variant was weighted to reflect the presence of the minor allele (A1). Homozygote minor allele carriers were coded as '2' in the dataset, heterozygotes as '1', and homozygote major allele carriers as '0'. However, as there were no minor allele carriers for rs25531, this variant was coded to reflect the presence of the minor 'G' allele, with heterozygotes coded as '1' and homozygote major 'A' allele carriers as '0'.

4.3.4.1. Genetic effects on cognitive biases

Two sets of analyses were used to test the association between the selected candidate sensitivity variants and each of the cognitive biases. In the primary analysis, a candidate sensitivity score (CSS) was created for each individual by summing the number of affect alleles from 23 of the 28 candidate sensitivity variants (five randomly removed due to LD). The association between this score and each of the cognitive biases, and their positive and negative components, was assessed using similar linear mixture models to those described above in **Section 4.3.2**. In the secondary analysis, similar models were used to explore the associations between each of the candidate sensitivity variants one at a time and each of the cognitive biases, including their positive and negative components.

Table 4.9. Descriptive statistics of candidate sensitivity variants

CHR	Gene	SNPs	Base Pair	A1	A2	Genotypes							HWE p-values	Q Values	MAF	Assay
						1/1	N	1/2	N	2/2	N	Total				
1	FAAH	rs324420	46870761	A	C	AA	17	AC	130	CC	244	391	1.000	1	0.210	Genotyped
1	NGF	rs6330	115829313	A	G	AA	63	AG	214	GG	114	391	**0.031***	0.167	0.435	Genotyped
3	OXTR	rs53576	8762685	A	G	AA	50	AG	183	GG	158	391	0.827	1	0.362	Imputed
3	GSK3B	rs6782799	119891946	T	C	TT	62	TC	189	CC	140	391	1.000	1	0.400	Imputed
4	NR3C2	rs5522	148436323	C	T	CC	3	CT	51	TT	337	391	0.446	1	0.073	Imputed
5	HTR1A	rs878567	63960164	G	A	GG	97	GA	183	AA	111	391	0.225	0.798	0.482	Imputed
6	FKBP5	rs3800373	35542476	C	A	CC	31	CA	167	AA	193	391	0.625	1	0.293	Genotyped
6	FKBP5	rs1360780	35607571	T	C	TT	35	TC	172	CC	184	391	0.636	1	0.310	Imputed
6	FKBP5	rs4713916	35669983	A	G	AA	36	AG	169	GG	186	391	0.906	1	0.308	Imputed
6	CNR1	rs7766029	88137716	T	C	TT	77	TC	190	CC	124	391	0.837	1	0.440	Imputed
6	CNR1	rs1049353	88853635	T	C	TT	40	TC	165	CC	186	391	0.725	1	0.313	Genotyped
6	OPRM1	rs1799971	154360797	G	A	GG	6	GA	92	AA	293	391	0.828	1	0.133	Genotyped
7	NPSR1	rs324981	34778501	T	A	TT	80	TA	206	AA	105	391	0.266	0.798	0.468	Imputed
11	TPH1	rs1800532	18047816	T	G	TT	74	TG	161	GG	156	391	**0.006***	0.101	0.395	Imputed
11	BDNF	rs6265	27679916	T	C	TT	16	TC	128	CC	247	391	1.000	1	0.205	Imputed
11	DRD2	rs1800497	113270828	A	G	AA	17	AG	120	GG	254	391	0.525	1	0.197	Imputed
11	HTR3A	rs1062613	113975284	T	C	TT	18	TC	142	CC	231	391	0.568	1	0.228	Imputed
12	TPH2	rs4570625	72331923	T	G	TT	20	TG	130	GG	241	391	0.656	1	0.217	Genotyped
13	HTR2A	rs6314	47409034	A	G	AA	1	AG	56	GG	334	391	0.710	1	0.074	Genotyped
13	HTR2A	rs6313	47469940	A	G	AA	47	AG	211	GG	133	391	**0.011***	0.101	0.390	Genotyped
13	HTR2A	rs6311	47471478	T	C	TT	47	TC	210	CC	134	391	**0.014***	0.101	0.389	Genotyped
16	SLC6A2	rs2242446	55690425	C	T	CC	45	CT	143	TT	203	391	**0.015***	0.101	0.298	Imputed
16	SLC6A2	rs5569	55697923	A	G	AA	50	AG	173	GG	168	391	0.580	1	0.349	Imputed
17	SLC6A4	5-HTTLPR	30237328	S	L	SS	71	SL	204	LL	116	391	0.261	0.798	0.443	Genotyped
17	SLC6A4	rs25531	30237328	G	A	GG	0	GA	348	AA	39	387	0.297	0.050	0.071	Genotyped
17	CRHR1	rs110402	43880047	A	G	AA	82	AG	193	GG	116	391	0.919	1	0.457	Imputed
20	CHRNA4	rs1044396	63349782	G	A	GG	77	GA	200	AA	114	391	0.610	1	0.453	Imputed
22	COMT	rs4680	19951271	G	A	GG	83	GA	177	AA	131	391	0.123	0.554	0.439	Genotyped

Note: The Table displays descriptive statistics for all candidate variants (SNPs), their chromosome (CHR), gene (Gene), and location (Base Pair). Also displayed are the alleles of each variant (A1 and A2), the number of individuals within each allelic group (Genotypes), plus the total number of individuals. Results of Hardy-Weinberg Equilibrium test (HWE P Value) and corresponding Q values are also included, as are minor allele frequencies (MAF) and information regarding whether a variant was genotyped or imputed (Assay).

Effects of the candidate sensitivity score on cognitive biases

Primary analysis revealed that only social interpretation bias was associated with the CSS. The association was positive, suggesting that those with a higher CSS had more negative biases in social interpretation. This finding also remained significant following correction for multiple testing (See **Table 4.10**). On exploring the positive and negative components of the biases, only the positive component of social interpretation (*positive social interpretation bias*) was found to be significant. Here, the association was negative, indicating those with a higher CSS reported fewer positive interpretations of social situations. This association was also shown to be significant following correction for multiple testing (see **Table 4.11**). In order to test whether the effects of the CSS were similar at each of the different timepoints, CSS-by-time interactions were included in the above models (see **Tables 4.10** and **4.11**). None of these interactions were significant for any of the biases tested suggesting that the effects of the CSS were similar across the three timepoints.

Table 4.10. Results of linear mixture models examining the effect of the candidate sensitivity score across time and by time, for all cognitive biases.

Cognitive biases	CSS across time			CSS by Time interactions		
	β	95% CI	P	β	95% CI	P
Memory bias	.02	(-.06-.09)	.704	.02	(-.03-.08)	.387
Non-social interpretation bias	.05	(-.03-.13)	.195	-.01	(-.07-.04)	.668
Social interpretation bias	.10	(.02-.18)	**.012* (.037)****	<.01	(-.06-.05)	.990

Note: The table displays beta coefficients, 95% confidence intervals and P-values of all candidate polygenic scores for each of the cognitive biases. Results marked with a single asterisk '*' represent a nominally significant finding *(p=0.05*), whilst those marked with a double asterisk '**' represent a significant finding following correction for multiple testing.

Table 4.11. Results of linear mixture models examining the effect of the candidate sensitivity score across time and by time, for the positive and negative components of the cognitive biases.

Cognitive bias components	CSS across time			CSS by Time interactions		
	β	95% CI	P	β	95% CI	P
Positive memory bias	-.04	(-.12-.04)	.287	<.01	(-.06-.05)	.895
Negative memory bias	.02	(-.05-.09)	.631	.02	(-.04-.08)	.576
Negative non-social interpretation bias	.03	(-.05-.11)	.430	-.02	(-.07-.04)	.595
Negative social interpretation bias	.06	(-.02-.14)	.139	-.02	(-.07-.04)	.597
Positive non-social interpretation bias	-.04	(-.12-.03)	.267	<.01	(-.06-.06)	.927
Positive social interpretation bias	-.11	(-.18--.03)	**.007* (.042)****	-.02	(-.08-.05)	.614

Note: The table displays beta coefficients, 95% confidence intervals and P-values of all candidate polygenic scores for each of the cognitive biases. Results marked with a single asterisk '*' represent a nominally significant finding *(p=0.05*), whilst those marked with a double asterisk '**' represent a significant finding following multiple testing corrections.

Effects of individual candidate sensitivity variants on cognitive biases

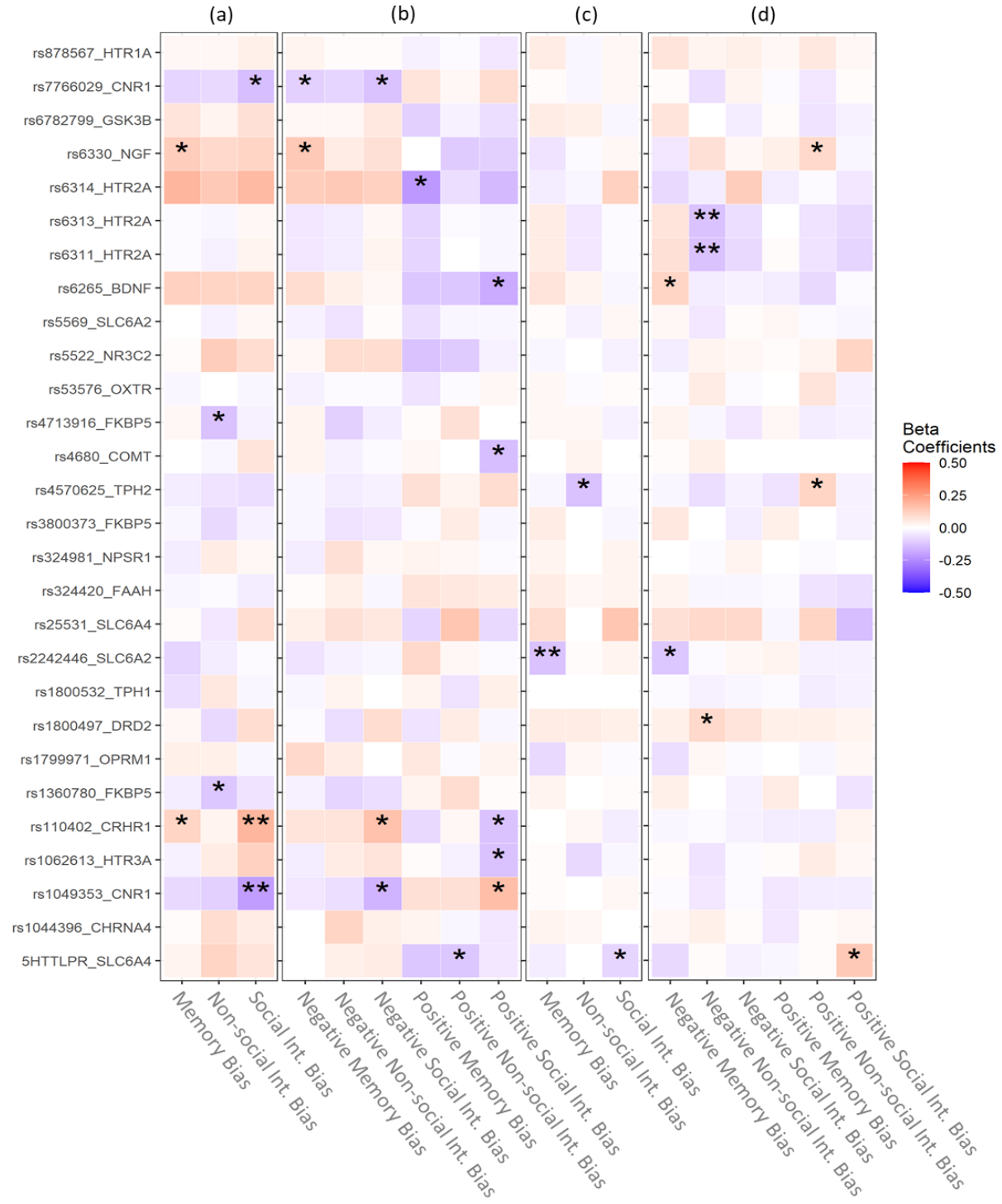
In the secondary analyses, the association between each of the individual candidate variants and each of the cognitive biases were tested one-by-one in separate linear mixed models (**Figure 4.1a-b**). There were 7 significant findings but only two survived correction for multiple testing: rs110402 in *CRHR1,* and rs1049353 in *CNR1*. Both were found to have significant associations with social interpretation bias. However, whilst rs110402 was found to have a positive association with social interpretation bias, rs1049353 had an opposing negative association with social interpretation bias. This suggests that those individuals with more sensitivity alleles at the rs110402 loci had a more negative social interpretation bias across the three timepoints, whilst those with more sensitivity alleles at the rs1049353 loci had a more positive social interpretation bias (**Figure 4.1a**). Further exploration of the positive and negative components of the biases

uncovered 12 nominally significant results (see **Figure 4.1b**). Interestingly, these included rs110402 in *CRHR1*, and rs1049353 in *CNR1*. In line with the above findings, rs110402 was associated with increases in the negative component of social interpretation bias (*negative social interpretation bias*), whilst rs1049353 was associated with increases in the positive component of social interpretation (*positive social interpretation bias*). However, neither finding survived multiple testing corrections.

In order to test whether the associations regarding the candidate sensitivity variants were similar across the three timepoints, genotype-by-timepoint interactions were included in the above models. These analyses uncovered three significant results across the three biases. However, only one remained significant following correction for multiple testing: the interaction between timepoint and rs2242446 in *SLC6A2* on memory bias (**Figure 4.1c**).

Genotype-by-time interactions were also tested for the positive and negative components of the biases (see **Figure 4.1d**) revealing 8 significant findings. However, only two remained significant following correction for the multiple testing: rs6313 and rs6311 in HTR2A, which both showed a significant interaction with timepoint on the negative component of non-social interpretation bias (*negative non-social interpretation bias*). Simple slopes analyses were used to further probe these interactions in which the linear effect of wave was tested separately for each genotype. This analysis including margin plots illustrating these effects can be found in **appendix (iii)**.

Figure 4.1. Displaying the effects of (a) genotype across time on cognitive biases, (b) genotype across time on positive and negative bias components, (c) genotype-by-time interactions on cognitive biases and (d) genotype-by-time interactions on positive and negative bias components.



Note: The coloured squares represent the beta coefficients/direction of effect. A single asterisk '*' represents a nominally significant result, a double asterisk '**' represents a result significant following multiple testing correction.

4.3.5. Effects of candidate sensitivity score-by-life event interactions on cognitive biases

In order to test whether the effects of life events on cognitive biases were moderated by the candidate sensitivity variants, the interaction between genotypes and life events was added as a fixed effect to models containing the separate fixed effects of both of these factors. Two sets of analyses were used to assess these genetic effects. In the primary analysis, the CSS described in the previous sections was used, while in the secondary analysis each of the candidate sensitivity variants were tested one by one in separate models for each of the cognitive biases and their positive and negative components. Results pertaining to these interaction analyses are given in **Table 4.12** and **Table 4.13** respectively.

Table 4.12. Results of linear mixture models examining the interaction between the candidate sensitivity score and negative and positive life events on each of the cognitive biases.

Cognitive biases	CSS-by-negative life events			CSS-by-positive life events		
	β	95% CI	P	β	95% CI	P
Memory bias	.03	(-.03-.08)	.363	.07	(.02-.13)	**.005* (.015)****
Non-social interpretation bias	.07	(.01-.13)	**.014* (.042)****	.05	(-.00-.10)	.058
Social interpretation bias	.02	(-.03-.08)	.412	.01	(-.04-.06)	.815

Note: The table displays beta coefficients, 95% confidence intervals and P-values of all candidate polygenic scores for each of the cognitive biases. Results marked with a single asterisk '*' represent a nominally significant finding (p=0.05), whilst those marked with a double asterisk '**' represent a significant finding following correction for multiple testing.

The CSS significantly moderated the association between negative life events and non-social interpretation bias. The association was positive, suggesting that those with a higher CSS had a stronger negative bias in non-social interpretation when experiencing negative life events. This interaction also survived correction for multiple testing (see **Table 4.12**). The CSS was also found to significantly moderate the association between positive life events and memory bias. This association was positive, indicating that those with a higher CSS had a stronger negative memory bias when experiencing positive life events. This finding also remained significant following correction for multiple testing (see **Table 4.12**). The significant interactions regarding negative

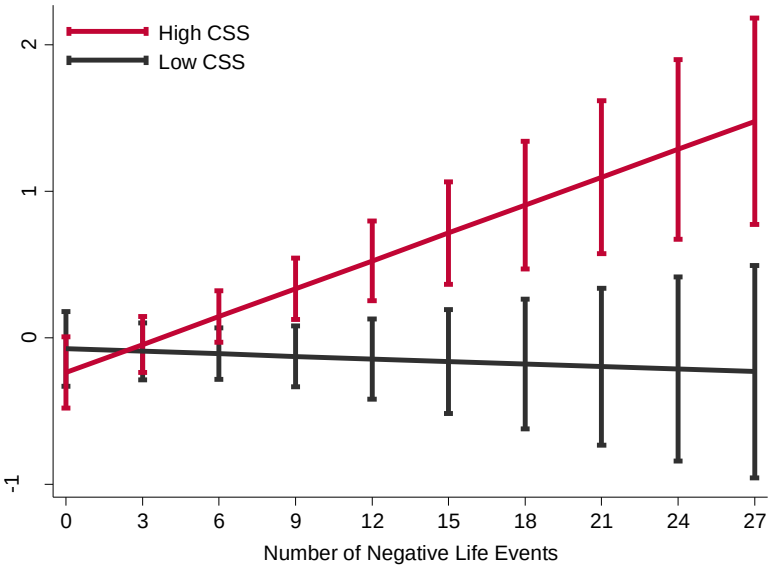
life events and non-social interpretation bias and positive life events and memory bias were further probed using simple slope analyses. In these analyses, the association between the number of negative life events on non-social interpretation bias and the number of positive life events on memory bias were tested in those with a high CSS (upper median split) and low CSS (lower median split).

For those in the high CSS group, there was a significant positive association between the number of negative life events and non-social interpretation bias (β=0.18, 95%CI=0.09-0.27, p=8.58x10^{-5}). However, for those in the low CSS group the number of negative life events was not significantly associated with non-social interpretation bias (β=0.07, 95%CI=-0.01-0.14, p=0.073). In contrast, the significant positive association between the number of positive life events and memory bias was found to be specific to those in the low CSS group (β=-0.12, 95%CI=-0.20--0.05, p=0.001). However, the number of positive life events was not significantly associated with memory bias in the high CSS group (β=0.01, 95%CI=-0.08-0.09, p=0.923). The associations between the number of negative life events and non-social interpretation bias, and the number of positive life events and memory bias in those with high and low CSS are further illustrated in **Figure 4.2** and **Figure 4.3** respectively.

In **Figure 4.2**, illustrating the association between negative life events and non-social interpretation bias, the fan-shaped interaction demonstrates that those in the high CSS group who had experienced no negative life events had a relatively similar non-social interpretation bias to those in the low CSS group. However as negative life events increase, a sharp increase in negative non-social interpretation bias is observed for those in the high CSS group. Conversely, an increase in the number of negative life events is shown as having no significant association with non-social interpretation bias for those in the low CSS group.

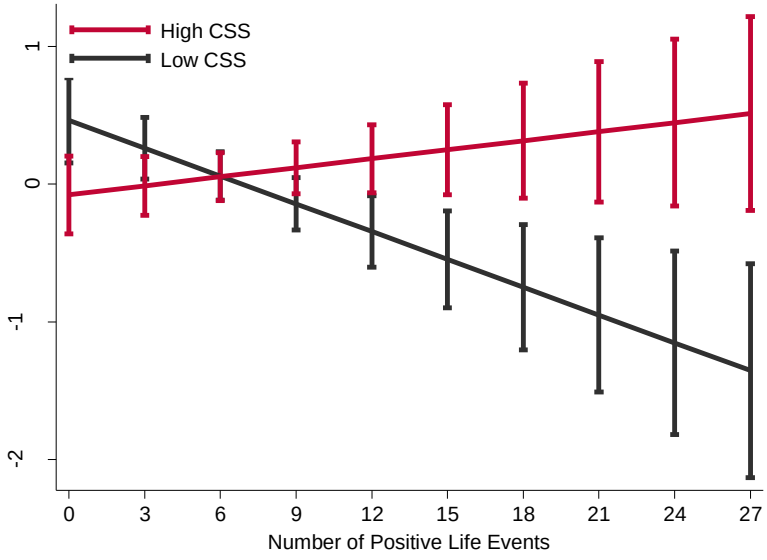
In the crossover interaction in **Figure 4.3,** illustrating the association between positive life events and memory bias, it can be seen that those in the low CSS group who had experienced no positive life events have a relatively negative memory bias compared to their high CSS counterparts. However, as positive life events increase in the low CSS group, a sharp increase in positive memory bias is observed. In contrast, for the high CSS group the number of positive life events experienced has no significant effect on memory bias.

Figure 4.2. Margin plot displaying the predicted effects of negative life events on non-social interpretation bias for those with a low and high candidate sensitivity score.



Note: The red line represents those with the highest median split CSS group, with the black line represents the lowest median split CSS group.

Figure 4.3. Margin plot displaying the predicted effects of positive life events on memory bias for those with a low and high candidate sensitivity score.



Note: The red line represents those with the highest median split CSS group, with the black line represents the lowest median split CSS group.

Interactions between life events and the CSS were further explored by considering the negative and positive components of the cognitive biases separately. The results of these analyses are given in **Table 4.13.**

Table 4.13. Results of linear mixture models examining the effect of the candidate sensitivity score by life event interactions, for the positive and negative components of the cognitive biases.

Cognitive bias components	CSS-by-negative life event Interaction			CSS-by-positive life event Interaction		
	β	95% CI	P	β	95% CI	P
Positive memory bias	-.04	(-.10-.01)	.133	-.06	(-.11--.01)	**.022*** (.120)
Negative memory bias	.01	(-.04-.07)	.628	.03	(-.02-.08)	.243
Negative non-social interpretation bias	.07	(.01-.12)	**.025*** (.151)	.02	(-.04-.07)	.563
Negative social interpretation bias	.02	(-.04-.07)	.516	-.01	(-.06-.04)	.561
Positive non-social interpretation bias	-.03	(-.09-.03)	.323	-.06	(-.11--.00)	**.040*** (.120)
Positive social interpretation bias	-.02	(-.08-.05)	.616	-.04	(-.10-.02)	.161

Note: The table displays beta coefficients, 95% confidence intervals and P-values of all candidate polygenic scores for each of the cognitive biases. Results marked with a single asterisk '*' represent a nominally significant finding (p=0.05), whilst those marked with a double asterisk '**' represent a significant finding following correction for multiple testing.

These analyses revealed no significant findings that survived correction for multiple testing regarding the interaction between the CSS and positive or negative life events on either the negative or positive components of the cognitive biases. However, there was a nominally significant interaction between the CSS and negative life events on the negative component of non-social interpretation bias (*negative non-social interpretation bias*). This association, albeit nominally significant was positive, suggesting that those with a higher CSS interpreted more non-social situations as negative in the SRET after experiencing increased numbers of negative life events. There was also a nominally significant interaction between the CSS and positive life events on the positive component of memory bias (*positive memory bias*). Although only nominally significant, the association was negative, indicating that those with a higher CSS endorsed and

recalled fewer positive words in the SRET despite experiencing positive life events. A nominally significant interaction was also observed for the interaction between the CSS and positive life events on the positive component of non-social interpretation bias (*positive non-social interpretation bias*). This nominally significant association was negative, indicating that those with a higher CSS interpreted less non-social situations as positive despite experiencing more positive life events.

Candidate sensitivity score-by-life event interactions: Sensitivity analysis

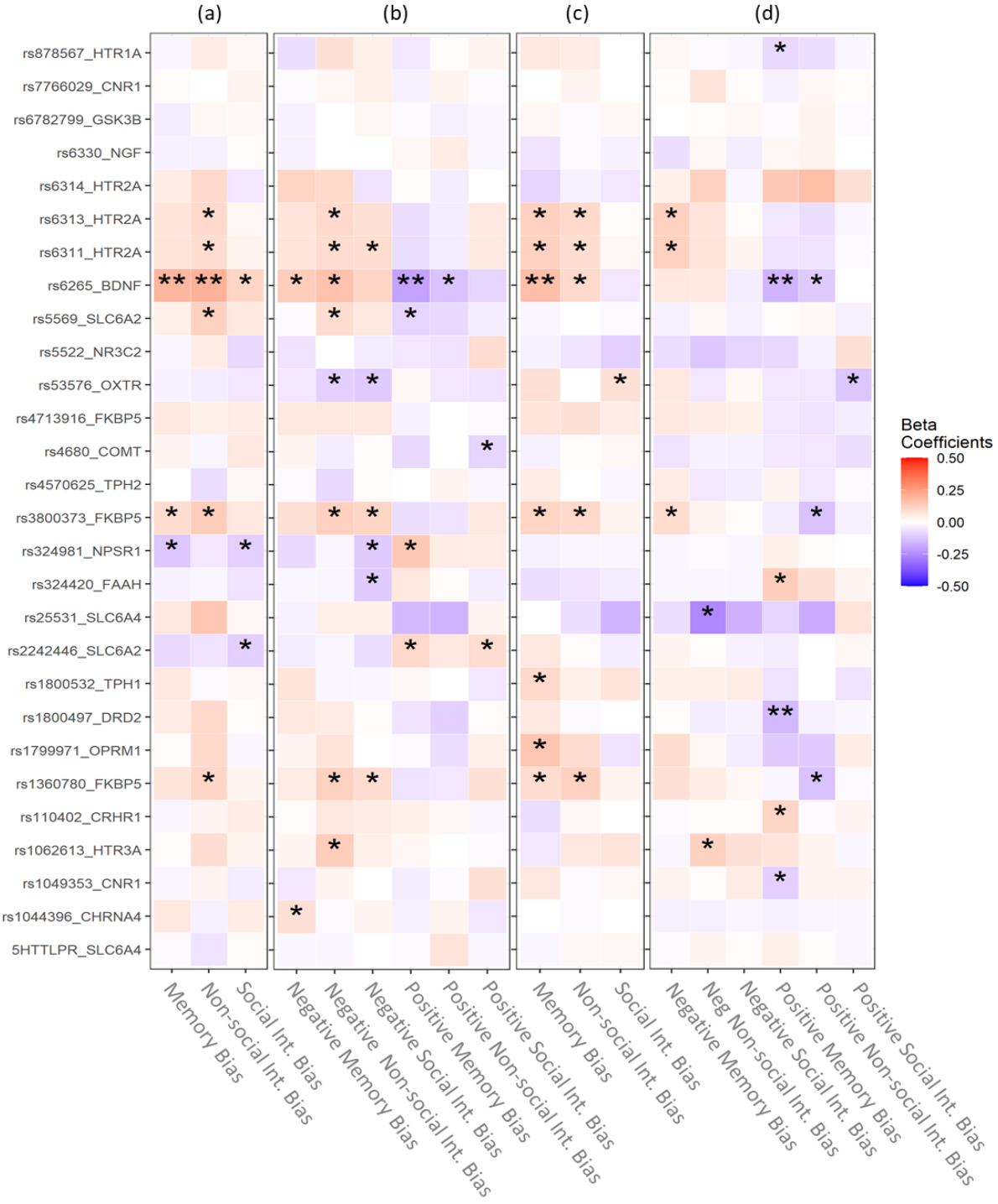
Analysis regarding the originally significant CSS-by-life events interaction was rerun using both the reduced 19-item subset CASE list, and the further reduced 11-item independent CASE list as described in **Section 4.3.3.1**. The previously significant interaction between negative life events and the CSS on non-social interpretation bias failed to remain significant when the reduced 19-item CASE list was used (β=0.04, 95%CI=-0.02-0.10, p=0.216). This was also true for the same interaction when using the 11-item independent CASE list (β=0.03, 95%CI=-0.02-0.09, p=0.260).

The significant interaction between positive life events and the CSS on memory bias remained significant when using the reduced 19-item CASE list, and also survived correction for multiple testing, (β=0.09, 95%CI=0.02-0.16, p=0.016, FDR=0.048). However, when using the 11-item independent CASE list, the interaction between positive life events and the CSS on memory bias was no longer significant (β=0.05, 95%CI=-0.03-0.12, p=0.213).

4.3.6. Effects of individual candidate sensitivity variants-by-life event interactions on cognitive biases

Secondary analysis regarding the interactions between each of the candidate sensitivity variants and positive and negative life events on each of the cognitive biases were tested in separate linear mixed models. The results of these analyses are given in **Figure 4.4**. This shows 62 significant results across 20 of the 28 candidate variants and across both cognitive biases and their positive and negative components. Six of these results remained significant following multiple testing correction: rs1800497 in DRD2 and rs6265 in BDNF.

Figure 4.4. Displaying the effects of (a) genotype-by-negative life events interaction on cognitive biases, (b) genotype-by-negative life events interaction on positive and negative bias components, (c) genotype by positive-life-events interaction on cognitive biases and (d) genotype-by-positive life events interaction on positive and negative bias components.



Note: The coloured squares represent the beta coefficients/direction of effect. A single asterisk '*' represents a nominally significant result, a double asterisk '**' represents a result significant following multiple testing correction.

Candidate sensitivity variant-by-negative life event interactions on cognitive biases

Secondary analysis regarding the candidate sensitivity variants-by-negative life event interactions uncovered 12 significant results with two surviving correction for multiple testing (see **Figure 4.4a**). These were the interactions between negative life events and rs6265 in BDNF on memory bias and between negative life events and rs6265 on non-social interpretation bias. Simple slope analyses were used to probe these significant interactions in more depth. In these analyses the association between negative life events and both memory bias and non-social interpretation bias were assessed separately in T-allele carriers (TT and CT) and those with the CC genotype for rs6265 in BDNF. The collapsing of the T-allele carriers into a single group was necessary due to the low number of homozygote T-allele carriers (n=16). This simple slope analyses including margin plots illustrating these effects can be found in **appendix (iv)**.

Candidate sensitivity variant-by-negative life event interactions regarding the negative and positive components of each of the cognitive biases uncovered 23 significant results with one surviving correction for multiple testing: the interaction between BDNF (rs6265) and negative life events on the positive component of memory bias (*positive memory bias*) (see **Figure 4.4b**). Simple slope analysis regarding this finding, including margin plots illustrating the associations, can be found in **appendix (iv)**.

Candidate sensitivity variant-by-positive life event interactions on cognitive biases

Secondary analysis regarding the interaction between positive life events and each of the candidate sensitivity variants on the cognitive biases revealed 13 nominally significant findings (see **Figure 4.4c**). However, BDNF (rs6265), was the only variant that survived correction for multiple testing, moderating the association between positive life events and memory bias. Simple slope analysis regarding this finding, including margin plots illustrating the associations, can be found in **appendix (v)**.

The effect of positive life events on the positive and negative components of the cognitive biases highlighted 15 nominally significant findings, two of which survived correction for multiple testing (see **Figure 4.4d**). These included BDNF (rs6265) and DRD2 (rs1800497), which both

moderated the association between positive life events on the positive component of memory bias (*positive memory bias*). As with BDNF (rs6265), DRD2 (rs1800497) AG and AA genotype were collapsed into a single genotypic group due to low numbers of homozygote A-allele carriers within the sample (n=17). Again, simple slope analysis including margin plots illustrating these associations can be found in **appendix (v)**.

Effects of individual candidate sensitivity variant-by-life event interactions on cognitive biases: Sensitivity analyses

All secondary analysis regarding each candidate sensitivity variant-by-life event interaction was rerun using both the 19-item CASE list, and the further reduced 11-item CASE list as described above. Results from these analyses will now be discussed with particular reference to the previously significant finding from the primary results using all 38 CASE items.

Analysis regarding each of the candidate sensitivity variants, and their interaction with the number of negative life events from the reduced 19-item list of CASE life events revealed two of the originally significant findings as remaining nominally significant, with the third original finding remaining significant following correction for multiple testing. The interaction between rs6265 and negative life events remained nominally significant for memory bias (β=0.16, 95%CI=0.04-0.28, p=0.007, FDR=0.196), and for the positive component of memory bias (*positive memory bias*: β=-0.13, 95%CI=-0.25--0.01, p=0.036, FDR=0.418). This interaction also survived multiple testing correction with regards to non-social interpretation bias (β=0.19, 95%CI=0.07-0.30, p=0.002, FDR=0.044).

Analyses regarding the number of positive life events from the same reduced 19-item CASE list was not as successful, with only two of the original three significant finding remaining nominally significant. The interaction between rs6265 and positive life events remained nominally significant for memory bias (β=0.11, 95%CI=0.00-0.22, p=0.042, FDR=0.167), as it did for the positive component of memory bias (*positive memory bias*) (β=-0.16, 95%CI=-0.27--0.05), p=0.004, FDR=0.085). The lack of a nominal or otherwise significant finding for the rs1800497-by-positive life event interaction regarding the positive component of memory bias (*positive memory bias*) when using the 19-item CASE list may indicate that it was a spurious finding.

Analyses regarding each of the candidate sensitivity variants, and their interaction with the number of negative life events using the 11-item CASE list revealed only one nominally significant result from the original three significant findings. The interaction between the variant rs6265 and negative life event remained nominally significant for the cognitive bias non-social interpretation bias (β=0.14, 95%CI=0.03-0.25, p=0.013, FDR=0.362). All other previously significant findings, including those for the cognitive bias memory bias, and the positive component of memory bias (*positive memory bias*) failing to reach nominal significance.

Results regarding each of the originally significant candidate sensitivity variants-by-positive life events using the 11-item CASE list uncovered no significant findings, nominally or otherwise.

4.3.7. Gene-environment correlation analysis

To ensure that the above gene-by-life event interaction analysis did not violate any interaction assumptions, the correlations between each candidate sensitivity variant and both negative and positive life events were assessed. Poisson regressions were performed, using the same covariates of age and sex, revealing that only one variant amongst all 28 had a significant association with negative life events (rs324981: β=.13, p=.007). All other variants, including those that were shown to have a significant interaction with both negative and positive life events, were shown to have no significant associations with either negative or positive life events. The same analysis was also conducted to examine whether there were any confounding correlations between the CSS and life events that may have impacted on the significant findings. Using the same Poisson regressions, and covarying for both age and sex, analysis revealed no significant correlations between life events and the CSS

4.3.8. Effects of Psychopathology

Using the same originally constructed mixture models the fixed effects of anxiety and depression were included as covariates. This was done for all significant findings across both the cognitive biases and their positive and negative components using data collected from each timepoint using the Revised Children's Anxiety and Depression Scale - Short Form (RCADS-SF).

Main effects of life events on cognitive biases: Controlling for psychopathology

All previously significant associations between negative life events and cognitive biases were found to be driven by depression and anxiety scores. These included memory bias (β=0.003, 95%CI=-0.04-0.05, p=0.888), social interpretation bias (β=-0.03, 95%CI=-0.07-0.02, p=0.274) and non-social interpretation bias (β=0.03, 95%CI=-0.03-0.08, p=0.333). This was also true for the association between negative life events and the interpretation bias components *negative social interpretation bias* (β=0.02, 95%CI=-0.03-0.07, p=0.398), and *negative non-social interpretation bias* (β=0.04, 95%CI=-0.02-0.09, p=0.183). All other main effects of life events (both positive and negative) on the cognitive biases and their positive and negative components remained significant, showing little change, suggesting that these results were significant above and beyond the effects of these psychopathologies.

Main effects of the candidate sensitivity score on cognitive biases: Controlling for psychopathology

The initial significant association between the CSS and social interpretation bias remained significant when controlling for both depression and anxiety (β=0.09, 95%CI=0.02-0.15, p=0.014). This was also true for the association between the CSS and bias component positive social interpretation (β=-0.10, 95%CI=-0.18--0.03, p=0.008), suggesting, in both cases, that the effect of the CSS remains a significant factor despite symptoms of these psychopathologies.

Main effects of the individual candidate sensitivity variants on cognitive biases: Controlling for psychopathology

The effects of anxiety and depression were also found to be the driving force behind the only two individual candidate sensitivity variants found to have a significant direct association with the cognitive biases. The effect of both CRHR1 (rs110402) and CNR1 (rs1045393) on memory bias were found to drop out of significance when controlling for the fixed effects of anxiety and depression symptoms respectfully (rs110402: β=0.06, 95%CI=-0.02-0.14, p=0.139; rs1045393: β=-0.03, 95%CI=-0.12-0.05, p=0.459).

Interaction effects of the candidate sensitivity score on cognitive biases: Controlling for psychopathology

The significant interaction between the CSS and negative life events on non-social interpretation bias was no longer significant, when controlling for the effects of both depression and anxiety (β=0.05, 95%CI=-0.01-0.10, p=0.091). However, the significant interaction between the CSS and positive life events on memory bias did remained significant, with little change, when controlling for the effects of both depression and anxiety (β=0.06, 95%CI=0.02-0.11, p=0.004). This suggests that the initial significant interaction between the CSS and negative life events on non-social interpretation bias was likely driven, in part by existing depression and anxiety symptoms. However, the interaction between the CSS and positive life events on memory bias are shown here to be significant irrespective of any symptoms of these psychopathology.

Interaction effects of the individual candidate sensitivity variants on cognitive biases: Controlling for psychopathology

Of the three candidate sensitivity variants-by-time interactions that were significant in the original analysis, all remained significant after controlling for the effects of depression and anxiety. The interaction of rs6311 and rs6313 in HTR2A-by-time on the bias component *negative non-social interpretation bias* were both found to retain their significance when covarying for psychopathology (rs6311: β=0.11, 95%CI=-0.19--0.03, p=0.008; rs6313: β=0.12, 95%CI=-0.20--0.03, p=0.006). This was also true for the rs2242446-by-time interaction on memory bias (β=0.13, 95%CI=-0.20--0.06, $p=2.8\text{x}10^{-4}$).

All six previously significant finding regarding the interaction between the individual candidate sensitivity variants and life events also remained significant when controlling for the effects of psychopathology. These interactions included the effect of rs6265-by-negative life events on memory bias (β=0.03, 95%CI=0.01-0.06, p=0.013), as well as the positive component of memory bias (*positive memory bias*) (β=-0.04, 95%CI=-0.07--0.01, p=0.007), and non-social interpretation bias (β=0.05, 95%CI=0.02-0.08, p=0.001). These findings also remained significant for the interaction between rs6265 and positive life events on both memory bias (β=0.05, 95%CI=0.02-0.08, p=0.001), and the positive component of memory bias (*positive memory bias*) (β=-0.05, 95%CI=-0.08--0.02, p=0.002). Lastly the significant interaction between rs1800497 and

positive life events on the positive component of memory bias (*positive memory bias*) also remained significant (β=0.05, 95%CI=-0.09-0.02, p=0.001). These findings suggest that the original associations were not driven by symptoms of depression and anxiety.

4.4. Discussion

The aim of the current study was to provide a comprehensive test of the recently proposed CogBIAS hypothesis (Fox & Beevers, 2016). More specifically, the effects of positive and negative life events, variants previously implicated in GxE studies of depression and anxiety and the interplay between these factors were tested as predictors of attention, interpretation and memory biases. This was assessed in a sample of 12-16-year-old children tested over three time points as part of the CogBIAS-L-S (Booth et al., 2017). The hypotheses and results relating to these aims are discussed in detail below.

4.4.1. Life events and cognitive biases

In line with the primary hypothesis, negative life events were associated with more negative memory, social interpretation and non-social interpretation biases. Interestingly, these effects appeared to be driven by the specific association with negative, but not positive, components of these biases. These findings replicate those from previous studies whereby stressful life events, both dependent and independent in nature, have been shown to increase anxiety sensitivity over time (Zavos, Wong, et al., 2012).

It was also found that the effects of negative life events were relatively stable over time. Thus, time-by-life event interactions were non-significant for all biases except the negative component of memory bias (*negative memory bias*) in which life events appeared to have an increasing effect over time. Very few studies have explored the effects of life events on cognitive biases longitudinally. However, current findings are in keeping with the study by Zavos et al. (Zavos, Wong, et al., 2012) that found a similar effect of dependant and independent stressful life events on increasing anxiety sensitivity over three time points. However, further research is required to ascertain whether this finding can be replicated, and whether it is specific only to the negative component of memory bias.

It is unclear why negative life events had an increasing effect on the negative component of memory bias from early to late adolescence in the current sample. However, one possible explanation is that there are many changes in the type and frequency of life events throughout this developmentally sensitivity period. New life events begin to come into play as a result of everyday changes including increased responsibilities, higher-level education, more complex social

interactions, and puberty amongst others. However, another reason could be that depression tends to increase during this period. In line with this suggestion, a recent publication examining the trajectory of phenotypes within the current sample did highlight increasing depression symptoms across the CogBIAS-L-S (Booth, Songco, Parsons, Heathcote, & Fox, 2019). Nevertheless, more research is required to assess these developmental changes, and whether new developmentally dependant life events could have an increasing impact on this memory bias component.

The current study also included, for the first time, analysis of the relationship between positive life events and cognitive biases. It was hypothesised that perceived positive life events would be associated with more positive and less negative cognitive biases. In line with this hypothesis, positive life events were significantly associated with more positive memory and social interpretation biases. Interestingly, these effects appeared to be driven by the specific association with positive, but not negative, components of these biases. This is a completely novel finding that requires replication. To date, no studies have assessed the effects of positive life events on cognitive biases, or their positive and negative components. Also, in line with the hypothesis, the effects of positive life events were stable over time showing no significant time-by-life event interactions.

Positive and negative life events have both been implicated in the development of psychopathologies such as depression (Bouma, Ormel, Verhulst, & Oldehinkel, 2008), anxiety (Phillips, Hammen, Brennan, Najman, & Bor, 2005), as well as subjective wellbeing (Suh, Diener, & Fujita, 1996). Indeed, negative and stressful life events have been shown to increase momentary mood reactivity leading to depressed mood (Schneiders et al., 2006), whilst positive life events have been shown to buffer against stress related depressive symptoms (Dixon & Reid, 2000) and increase life satisfaction (McCullough, Huebner, & Laughlin, 2000). Findings from the current study suggest that these effects might be mediated by negative or positive cognitive biases.

The CASE life event measure required that each participant rated whether each life event they endorsed was positive or negative. Therefore, it is plausible that associations between life events and cognitive biases were not necessarily the result of differences in *occurrence* but rather *interpretation* of each of the life events as either positive or negative. In order to explore this possibility, sensitivity analyses were conducted using a reduced 19-item CASE, which excluded any events in which the positive or negative rating was associated with cognitive biases. Using

this reduced list, the associations between positive life events and the biases remained significant, and similar to those using the full CASE list. However, the associations between negative life events and cognitive biases remained significant only for memory bias, the negative components of memory bias (*negative memory bias*) and the negative component of social interpretation bias (*negative social interpretation bias*). These findings suggest that there may be a confounding effect of the interpretation and reporting of negative, but not positive life events. This bias in the reporting of negative life events across the original findings may have been a reflection of the 19 CASE items that were removed. For example, of the 19 items removed from the full CASE the majority were somewhat ambiguous (e.g. 'I stayed away from home overnight', or 'I changed school'), and others more negative ('I did badly in an important test or exam', or 'Someone special to me died (who was not in your family)'), with only three items being clearly positive ('I (or my team) won a prize, award or contest', 'I got a new boyfriend or girlfriend', 'I made a new special friend'). Therefore, it is possible that those with pre-existing negative biases who had interpreted and reported these ambiguous and negative life events as more negative and severe, respectively, had also been driving the original significant association with negative life events.

It is also plausible that any association between life events and cognitive biases are the result of reverse causality, with cognitive biases influencing life events rather than life events influencing cognitive biases. In order to explore this possibility, further sensitivity analyses were conducted excluding any dependent events that could have been the result of the participants' behaviour. Using this 11-item list of relatively independent life events had a substantial impact on the results. Specifically, negative life events were no longer associated with the three cognitive biases, although there remained a significant association with the negative components of social interpretation bias (*negative social interpretation bias*) and memory bias (*negative memory bias*), with only the latter remaining significant after correction for multiple testing. Positive life events were no longer associated with any of the biases or their positive components. This could suggest that the previous significant associations between positive life events, cognitive biases, and their components, were the result of reverse causality. That is, those with a more positive bias led to them experiencing more positive life events due to the behavioural dependant effects of their biases. However, with a reduction from 38 to eleven CASE items it could also be that such a decrease in power had simply rendered the detection of these effects highly unlikely. However, despite this, the interaction between life events and time on the number of negative words endorsed

and recalled in the SRET (*negative memory bias*) remained significant using the 19-item CASE, and nominally significant using the 11-item CASE, suggesting that these findings were robust to biases in the interpretation of life events or reverse causality.

Further research is needed to investigate these associations in a much larger independent sample using a cross-lagged mediation model, as this would also allow for potential causal effects to be assessed more reliably. This could also include a more balanced life events inventory with regards to the amount of dependent and independent life events such as the Life Event Scale for Adolescents (LES-A) (Coddington, 1984), used by Zavos et al. (2012) who also found similar effects.

In summary, the current study demonstrates, in line with previous research highlighted above, (Connolly & Alloy, 2018; Dearing & Gotlib, 2009; Joormann et al., 2015), that both positive and negative life events, have stable associations with cognitive biases, independently driving increases in positive and negative memory and interpretation biases. However, whilst sensitivity analysis involving the 19-item CASE revealed that the associations between positive life events and cognitive biases were somewhat robust, the same could not be said for negative life events, as many of these associations were lost. It could be suggested that for negative life events, association with cognitive biases were dependant on a negative bias in the reporting of ambiguous events as well as a negative bias for reporting an increased severity of negative events. Although, as the 11-item CASE sensitivity analysis demonstrated, associations between positive life events and the cognitive biases, as well as their components, may have been the result of reverse causality as a result of behavioural dependant effects. Nevertheless, the negative component of memory bias (*negative memory bias*), held up as significant, following multiple testing corrections, at all stages of sensitivity analysis highlighting the robustness of this finding.

4.4.2. Genetic associations with cognitive biases

It was hypothesised that there would be an association between genetic variants implicated to increase sensitivity to environmental effects in GxE studies of depression and anxiety and each of the cognitive biases. This was tested through primary analysis assessing the cumulative effect of all included candidate sensitivity variants in a CSS, as well as secondary analysis assessing each of the candidate sensitivity variants individually.

In line with the hypothesis, the CSS was significantly associated with a more negative social interpretation bias that remained significant following correction for multiple testing. Analyses of the positive and negative components of this measure suggested that this significant finding was not driven by an increase in negative interpretations of social scenarios, but rather a significant *lack of positive interpretations* of these scenarios, which also survived correction for multiple testing. There were no significant associations between the CSS and memory or non-social interpretation bias. Furthermore, there were no significant CSS-by-time interactions suggesting that the effects of the CSS were similar at 12, 14, and 16 years of age across all biases and their positive and negative components.

As discussed earlier, previous studies have shown that cognitive biases are heritable (Eley et al., 2008). Furthermore, the same genetic variants implicated to increase sensitivity to environmental effects in GxE studies of depression and anxiety, have also shown significant associations with cognitive biases, including interpretation bias (Fox & Standage, 2012). However, further replication is required, given that the current study is the first to test the cumulative effects of selected candidate sensitivity variants on cognitive biases, an approach which provides increased statistical power, and represents a particular strength of the current study.

The finding that the significant association between the CSS and a more negative social interpretation bias was specific to the positive, but not the negative component of social interpretation bias was unexpected. However, this is an important finding as it demonstrates that the positive and negative aspects of these biases are not two sides of the same coin – in that a negative bias is not the same as an absence of a positive bias.

Previous literature in this area is relatively scarce, as whilst there have been several studies demonstrating the effect of single candidate variants on specific negative cognitive biases (Beevers et al., 2009; Fani et al., 2013; Fox & Standage, 2012; Pergamin-Hight et al., 2012), few have assessed associations with positive cognitive biases (Fox et al., 2009; Gong et al., 2013). Therefore, more research is required to replicate these findings in larger independent samples.

Taken together, these results provide partial support for the CogBIAS Hypothesis (Fox & Beevers, 2016), although in contrast to the hypothesis, findings appear to be specific to the positive aspects of social interpretation bias. These findings also suggest that a lack of positive social interpretation bias is a potential mechanism through which such sensitivity variants increase the

risk of anxiety or depression in the context of a negative environment. However, further research is required to examine the reliability of these findings and their implications for the CogBIAS Hypothesis.

In secondary analyses regarding the associations between the individual candidate sensitivity variants and cognitive biases, none of the sensitivity variants previously associated with individual differences in cognitive biases showed associations that survived correction for multiple testing including 5-HTTLPR and rs25531, as well as variants in COMT, DRD2, FKBP5, or BDNF. However, with the exception of rs3800373 in FKBP5, and rs25531 there were nominally significant associations across the majority of these variants. For example, analyses highlighted a nominally significant association between 5-HTTLPR and positive non-social interpretation bias, as well as a nominally significant interaction between 5-HTTLPR and time on both social interpretation bias and its positive component (*positive social interpretation bias*). Rs4680 in COMT also showed a nominally significant association with the positive component of social interpretation bias (*positive social interpretation bias*), as did rs6265 in BDNF. There was also a nominally significant interaction between Rs6265 in BDNF and time on the negative component of memory bias (*negative memory bias*), and rs1800497 in DRD2 on the negative component of non-social interpretation bias (*negative non-social interpretation bias*). Rs1360780 and rs4713916 both in FKBP5 also demonstrated a nominally significant association with non-social interpretation bias. Whilst noteworthy, these associations are subject to replication, as whilst the current study may have been too underpowered for the associations to survive correction for multiple testing, past research regarding these variants have not always produced consistent findings.

The only two candidate sensitivity variants that survived correction for multiple testing were rs1049353, a SNP in the Cannabinoid receptor 1 (CNR1) gene, and rs110402, located in the Corticotropin-Releasing Hormone Receptor 1 (CRHR1) gene, both of which showed a significant association with social interpretation bias.

The association between rs1049353 and social interpretation bias was in the expected direction. That is, the major C-allele (also described as G in previous studies using the forward strand coding), which has been shown to confer increased sensitivity to the environment, was associated with a more negative social interpretation bias. This finding is in keeping with a recent

study (Agrawal et al., 2012) which suggested that rs1049353 moderated the association between childhood physical abuse on anhedonic depression in a sample of young American women and an independent Australian sample (Agrawal et al., 2012). In both samples, carriers of the minor A-allele (T in the current study) showed less anhedonic depression following childhood physical abuse, than those homozygous for the major G-allele (C in the current study). Unsurprisingly, anhedonia, which refers to an inability to experience pleasure and joy from stimuli or activities that would normally be considered joyful, has been positively correlated with a negative interpretation bias (Pictet, Jermann, & Ceschi, 2016). Taken together the current study can be seen to support this association as the C-allele was associated with an *increased* negative bias for social interpretation.

However, more research is required to replicate this main effect between rs1049353 and social interpretation bias, as research regarding this association is very limited. Furthermore, the variant rs1049353 is exonic yet synonymous, meaning that whilst it enhances accurate splicing of RNA into messenger RNA (mRNA), it does not cause a change to the amino acid, specifically indicating that the effect it has on the activity of CNR1 is not related to a coding change. Despite this, synonymous single nucleotide polymorphisms are able to cause changes in the formation of proteins, and there is evidence that the location of rs1049353 is within an exon splicing enhancer that recruits spliceosomes and other necessary systems to splice exons throughout translation (Solis, Shariat, & Patton, 2008). Therefore, further research should also assess the A allele carrier genotypes (A/A and A/G) of rs1049353 and their association with changes in endocannabinoid activity.

Findings for rs110402 in CRHR1, were also in the expected direction. That is the A-allele, which has been previously shown to confer sensitivity to childhood maltreatment, was associated with an increased negative social interpretation bias. While this was the first study to explore the involvement of this variant in the development of cognitive biases, a recent study did investigate the role of rs110402 in the cognitive symptoms of depression (E. G. Davis et al., 2018). Here, it was found that a haplotype containing the A-allele of rs110402 was associated with the cognitive symptoms of depression including difficulty with decision-making, higher rumination, and poorer learning and memory. Taken together these findings suggest that negative social interpretation biases may explain why the effects of maltreatment appear to be greater for A-allele carriers in GxE studies of depression and anxiety (Nugent, Tyrka, Carpenter, & Price, 2011). However,

further research is required to assess this association across time in a longitudinal dataset and establish whether it does indeed increase a negative bias in social interpretation.

In order to test whether the effects of the selected candidate sensitivity variants were similar across the three timepoints, candidate sensitivity variant-by-time interactions were also tested. Only three selected candidate sensitivity variants showed significant interactions with time that survived correction for multiple testing: rs2242446 in SLC6A2 and, rs6313 and rs6311 in HTR2A.

Probing of the rs2242446-by-time interaction showed that there was no association between this variant and memory bias at the initial assessment (at age 12), but by the third assessment (at age 16) the T-allele at this locus was associated with negative memory biases. Findings were similar for rs6313. While there was little effect of genotype at the initial assessment (at age 12), by the third assessment (at age 16) the A-allele at this locus was associated with fewer negative interpretations of non-social situations. Findings were nearly identical for rs6311 as a result of the high LD between these variants.

While these associations were modest and only observed as significant at timepoint three, this increase in significance from 12 to 16 years of age for both of these variants could suggest a developmentally specific effect. Indeed, twin studies suggest that different genetic factors influence symptoms of both depression and anxiety throughout development (Kellough, Beevers, Ellis, & Wells, 2008) and demonstrate new genetic factors coming online as well as distinct and influential environmental factors either reducing or increasing with age. The interactions regarding these variants could represent effects that are dependent on biological maturation as well as differences in major latent environmental factors.

Previous studies have not explored associations between rs2242446, rs6313 or rs6311 and cognitive biases, or how these change over time. While there are studies exploring the associations between these SNPs and MDD risk, they have provided conflicting results. Rs2242446 was first reported to be associated with MDD in a Chinese population (Cui, 2007) and supported by further studies using Asian samples (N. Sun et al., 2008; Wang et al., 2015; Xu et al., 2009). However, studies failed to replicate this finding in both Asian and non-Asian samples (Inoue, Itoh, Yoshida, Shimizu, & Suzuki, 2004; Pan, Cheng, Shan, & Yan, 2015; J. Sun, 2006; Ueda et al., 2016; Zill et al., 2002) resulting in two negative meta-analyses (Xiaofeng Zhao et al., 2013; Zhou, Su, Song, Guo, & Sun, 2014). Similarly, whilst one study suggested that the C-allele of rs6313 increases risk

of MDD (Du, Bakish, Lapierre, Ravindran, & Hrdina, 2000), another found that the same allele was protective (H.-Y. Zhang et al., 1997), with others finding no association (Khait et al., 2005; Kishi et al., 2009; Minov et al., 2001), also resulting in two negative meta-analyses (Anguelova, Benkelfat, & Turecki, 2003; Xue Zhao et al., 2014). Findings are also mixed for rs6311, with some studies reporting significant associations with MDD (Choi et al., 2004), including one meta-analysis (Xue Zhao et al., 2014), whilst others find negative associations (Kishi et al., 2009; Tencomnao, Thongrakard, Phuchana, Sritharathikhun, & Suttirat, 2010). It may be the case that these past conflicting results are the cause of individual difference in latent cognitive biases within the samples, ultimately driving the differences in observed associations between these variants and MDD. Alternatively, it may be that variations in age and ethnicity between studies were the cause of these contradictory findings.

Despite such discrepant findings, the current results could be seen to be in line with the majority of previous research demonstrating a negative association between both rs6313 and rs6311, and MDD (Khait et al., 2005; Kishi et al., 2009; Minov et al., 2001; Tencomnao et al., 2010), as both variants were shown to have a negative association seemingly protecting against a negative non-social interpretation bias. As a result, it could be postulated that these variants could protect against an outcome of depression by reducing or protecting against a negative bias in non-social interpretation. However, with research dampened by inconsistent findings, and with the current finding somewhat inconclusive, more research is required to assess the possible protective effects of these closely related variants in terms of MDD and negative biases in non-social interpretation, as well as any potential interplay between these variants and phenotypes.

4.4.3. Gene-environment interaction analyses

It was hypothesised that the association between negative and positive life events and cognitive biases would be moderated by genetic variants previously implicated to increase sensitivity to environmental effects in GxE studies of depression and anxiety. Specifically, it was expected that participants carrying more affect alleles of the selected candidate sensitivity variants, would show increased negative biases and decreased positive biases in the presence of negative life events, and increased positive biases and decreased negative biases in the presence of positive life events. These gene-environment interactions were tested in primary analysis by exploring the

interaction between the CSS and life events, before secondary analysis assessed each of the candidate sensitivity variants individually in the same GxE models.

In line with the hypothesis, the CSS significantly moderated the effects of negative life events on non-social interpretation bias and positive life events on memory bias, both of which survived correction for multiple testing. As expected, the moderation of negative life events by the CSS on non-social interpretation bias was found to be specific to the high CSS group with negative life events increasing a negative non-social interpretation bias in those carrying more sensitivity alleles. Furthermore, this interaction appeared to be driven by the negative component of this bias (*negative non-social interpretation bias*), with negative life events increasing the number of negative interpretations of non-social scenarios. The CSS also moderated the effect of positive life events on memory bias with associations driven by the positive component of this bias (*positive memory bias*), such that positive life events reduced the number of positive words endorsed and recalled in the SRET. However, upon further inspection and contrary to the hypothesis, the association was specific to the *low* CSS group, in that an increase of positive life events increased a positive memory bias in those with fewer sensitivity alleles. Also contrary to the hypothesis, there was no evidence that the CSS moderated the effects of negative life events on memory bias or positive life events on non-social interpretation bias. However, a nominally significant interaction was observed between the CSS and positive life events on the positive component of non-social interpretation bias (*positive non-social interpretation bias*).

The interaction between the CSS and negative life events on non-social interpretation bias was consistent with the current hypothesis, being both in the expected direction and found in the expected CSS group. This was evident as the association with negative life events increased a negative non-social interpretation bias for those in the high, but not those in the low CSS group. Furthermore, a fan-shaped interaction was observed suggesting that there was no significant difference between the low and high CSS groups in the absence of negative life events. This finding indicates that the effect of negative life events on non-social interpretation bias was specific to those in the high CSS group.

Like non-social interpretation bias, the interaction between the CSS and positive life events on memory was in the expected direction, however unlike non-social interpretation bias it was not found in the expected CSS group. That is, in those with a high CSS, the number of positive life

events had little to no effects on memory bias. However, for those with a *low* CSS the number of positive life events had a clear positive effect, with increases in the number of positive life events correlating with a more positive memory bias. Of particular interest was that there was evidence for a cross-over interaction, which may also explain the initial finding being driven by the negative effect, or absence of, the positive component of memory bias (*positive memory bias*). That is, when experiencing no positive life events those with a low CSS had a more negative bias than their high CSS counterparts. Taken together these findings suggest that whilst the low CSS group benefitted more from the effects of positive life events, they were also shown to have the worst outcome in the absence of these enhancing environments when compared to their high CSS counterparts.

In broad terms the interaction between the CSS and positive life events on memory bias was partially in line with the Differential Susceptibility hypothesis (DST) (Jay Belsky, 1997; J Belsky, 2005; Jay Belsky, Bakermans-Kranenburg, et al., 2007; Jay Belsky & Pluess, 2009a, 2013) which suggests that certain genetic variants increase sensitivity to both negative *and* positive environmental influences for better and for worse. However, in stark contrast to the Differential Susceptibility Hypothesis, it was the low susceptibility group that demonstrated this significant GxE effect on memory bias. Furthermore, although those in the low CSS group had a worse memory bias than those in the high CSS group in the absence of positive life events there was no such effect in terms of negative life events. Therefore, as only those in the low sensitivity group benefitted from the positive effects of greater numbers of positive life events on the development of an 'enhancing' bias, this effect should be interpreted as more in keeping with Vantage Sensitivity. Whilst this finding does provide some support for the concepts of the CogBIAS hypothesis (Fox & Beevers, 2016), it also violates one of its fundamental components.

The moderation of negative life events by the CSS on non-social interpretation bias showed no evidence to suggest an association in keeping with the Differential Susceptibility Hypothesis. However, the association did show some evidence in keeping with a pattern of Diathesis Stress as only the high CSS group experienced the detrimental effects of increased numbers of negative life events. This finding was in line with the assumptions of the CogBIAS hypothesis (Fox & Beevers, 2016), as genetic variants implicated to enhance sensitivity to environmental effects did significantly increase the negative effects of negative life events on the development of 'toxic' biases.

Whilst purely speculative and requiring further investigation, it may be that some of the 'candidate sensitivity variants' selected were not *general* sensitivity variants but instead specific to either positive or negative environments. As these variants were selected based on negative environmental effects impacting on phenotypes such as depression and anxiety, it could be suggested that affect alleles on these variants specifically increase sensitivity to negative life events, and therefore are more in keeping with a Diathesis Stress pattern of GxE interaction. Conversely, the corresponding major alleles, may have a protective effect and behave more in keeping with a Vantage Sensitivity pattern of GxE interaction. However, despite this, the effects of the CSS did demonstrate the wider assumptions of CogBIAS hypothesis, in that positive and negative life events impact on the development of positive and negative bias respectively in those with specific genotypes.

Previous studies have already shown that candidate-gene based polygenic scores created from similar lists of 'sensitivity' variants moderate the association between adversity and mental health (Jay Belsky & Beaver, 2011; Jay Belsky et al., 2015; Jay Belsky & Pluess, 2009b). However, studies of cognitive biases are yet to take this approach and have only shown significant GxE associations for individual variants, such as the 5-HTTLPR. This study is therefore the first to show that a cumulative score of sensitivity variants moderates the association between life events and cognitive biases.

Additional sensitivity analyses revealed that the original interaction between the CSS and negative life events on non-social interpretation bias was not a robust finding. This was evident as the interaction was no longer significant, nominally or otherwise, when applying the 19-item CASE or the 11-item CASE lists. This suggests that initial findings were likely the result of both a negative bias in the reporting of life events and their severity, as well as the occurrence of negative life events that were dependent on one's behaviour. In contrast, there was good evidence for the validity of the original CSS interaction effect on memory bias, confirming that the CSS does moderate the association between positive life events and memory bias, increasing a positive bias in memory in those with fewer sensitivity alleles. This interaction held nominal significance in the sensitivity analysis using the 19-item CASE list. However, the interaction was no longer significant when using the 11-item CASE list suggesting that the 23 variants included in the CSS may be of importance in the formation of this bias in the presence of positive life events, but only for dependent life events. However, this finding is given further gravitas by the fact that the

positive direction of effect was relatively stable, with only a moderate drop between the 19-item and 11-item CASE lists analyses.

Secondary analyses regarding individual candidate sensitivity variants on cognitive biases, did not provide any evidence that the 5-HTTLPR moderated the effects of negative or positive life events on cognitive biases. This finding further adds to the inconsistencies regarding the moderation of life events by 5-HTTLPR on cognitive biases (Jenness et al., 2016; Johnson et al., 2010; Kruijt et al., 2014).

Despite this, rs4680 in COMT, the separately genotyped rs25531 in SLC6A4, and rs3800373 and rs1360780, both in FKBP5, did show some nominal significance. However, COMT (rs4680) and SLC6A4 (rs25531) were only nominally significant in moderating negative life events on the positive component of social interpretation bias (*positive social interpretation bias*), and positive life events on non-social interpretation bias respectively, suggesting that these may have been chance findings and unlikely to replicate. Conversely, both rs3800373 and rs1360780 in FKBP5 showed nominal significance in moderating positive and negative life events across multiple biases and components in interpretation and memory. As these variants were nominally significant across multiple cognitive bias and bias components, it is likely that these findings represent true associations that the study was simply underpowered to detect following corrections for multiple testing. Replication in a larger sample is required to confirm this possibility.

Elsewhere however, there was evidence for a significant GxE interaction for rs1800497 in DRD2. Specifically, rs1800497 in DRD2 moderated positive life events on the positive component of memory bias (*positive memory bias*). However, findings were not in the expected direction. That is, whilst positive life events had a strong positive association with the positive component of memory bias (*positive memory bias*) in those with no sensitivity alleles at this locus (GG genotypes), no significant association was found in those carrying these sensitivity allele (GA or AA genotypes). Whilst previous research concerning rs1800497 and any cognitive biases are scarce, attention bias has received some focus, with one study finding rs1800497 to be associated with a positive attention bias (Gong et al., 2013). However, the majority of past research involving the DRD2 polymorphism has predominantly focused on addiction (C. Davis & Loxton, 2013; Gorwood et al., 2012; Savitz et al., 2013), depression (Roetker et al., 2012; Savitz et al., 2013), and other mood disorders (L. Zhang, Hu, Li, Zhang, & Chen, 2014). Furthermore, previous

research examining rs1800497 as moderating life events has to date only examined negative or stressful events (Elovainio et al., 2007), to which findings in the current study concerning this variant were not significant. In addition, the rs1800497-by-positive life events interaction on the positive component of memory bias (*positive memory bias*) was no longer significant in sensitivity analyses using either the 19-item or 11-item version of the CASE suggesting that the original finding could have been the result of biases in the *interpretation* of these life events rather than their *occurrence*.

There was also strong evidence for the moderation of life events by rs6265 in BDNF across several biases and their positive and negative components. Rs6265 (also known as Val66Met) significantly moderated the effects of negative life events on memory bias and social interpretation bias. Both of these findings were in the expected direction. That is, negative life events had little effect on either bias in those with the least sensitive CC (Val/Val) genotype, a moderate effect in those with a CT (Val/Met) genotype and a strong negative effect in those with the most sensitive TT (Met/Met) genotypes. Interestingly, the same variant also moderated the effects of positive life events on memory bias. However, findings were not in the expected direction. That is, for the more sensitive TT (Met/Met) or CT (Val/Met) genotypes, positive life events had little association with memory biases, or the positive memory bias component (*positive memory bias*). However, in those with the least sensitive CC (Val/Val) genotypes, positive life events were associated with both a more positive memory bias and an increased number of positive words endorsed and recalled in the SRET task (*positive memory bias*).

While this is the first study to show GxE effects of rs6265 on interpretation biases or memory biases, findings are in line with a previous study of never depressed healthy young adults, in which researchers found that life stress was associated with greater rumination in heterozygote Met/Met carriers of rs6265 in BDNF when compared to the other genotypes (Clasen, Wells, Knopik, McGeary, & Beevers, 2011). Whilst the outcomes of rumination, and interpretation and memory bias are separate phenotypes, they are both heavily implicated in both depression (Raes, 2010; P. C. Watkins, Vache, Verney, & Mathews, 1996) and anxiety (Herrera, Montorio, Cabrera, & Botella, 2017; Raes, 2010), with recent research also demonstrating that stress-reactive rumination following negative life events is associated with increased negative memory biases (Connolly & Alloy, 2018).

These findings are also consistent with previous studies demonstrating significant main effects and GxE interaction effects regarding the Met allele on depression (G. W. Brown et al., 2014; Karege et al., 2002; van Winkel et al., 2014), anxiety (Jie Chen, Yu, Liu, Zhang, & Zhang, 2015; U. E. Lang et al., 2005), stress response (Perea, Paternina, Gomez, & Lattig, 2012) and aspects of memory (Molendijk et al., 2012; van Oostrom et al., 2012). The current results also provide several potential mechanisms to explain why Met allele carriers are more sensitive to the depressogenic effects of stressful life events than those with the Val/Val genotype. Specifically, negative environments may cause Met allele carriers to forget more positive information and interpret non-social information in a more negative way than those with those with the Val/Val genotype. At the same time, positive environments may cause those with the Val/Val genotype to remember more positive information than their Met allele counterparts.

The interactions reported above remained significant in sensitivity analysis using the 19-item CASE, suggesting that they were not affected by reporting biases caused by a cognitive bias. However, in sensitivity analysis using the 11-item CASE including exclusively independent events, only the interaction between rs6265 and negative life events on non-social interpretation remained significant. This suggests that the interactions between rs6265 and life events on memory bias may be, at least in part, the result of reverse causality between cognitive biases and negative life events. However, it is also possible that the non-significant effects here were the result of a lack of power combined with the limited number of individuals with the specific minor allele genotype for rs6265, potentially rendering the analysis underpowered to detect the effects of this and other previously significant results involving rs6265.

4.4.4. Effects of Psychopathology

Self-reported anxiety and depression scores were controlled for across all significant findings to examine the effects of psychopathology and assure that reported results were not being driven by symptoms of psychopathology. Results demonstrated that anxiety and depression scores significantly impacted on previous significant associations found between negative life events and all cognitive biases. This was also the case for negative life events and all the negative components of social and non-social interpretation biases. However, this was not the case for the association between negative life events and the negative component of memory bias (*negative memory bias*), which despite a considerable drop in effect size did remain significant. Interestingly, the significant

association regarding positive life events across both cognitive biases and their positive components were not significantly influenced by depression and anxiety. This seems to suggest that the association between positive life events and cognitive biases operate independently to anxiety and depression status. Past research has highlighted robust findings regarding a mood-congruent bias in memory within depressed individuals (Mathews & MacLeod, 2005a). Furthermore, whilst individuals with depression show preferential recall for negative stimuli compared to neutral, their preferential recall for positive stimuli over neutral stimuli tends to be lacking in comparison to non-depressed individuals. There is also the issue regarding how the information is initially encoded. For example, whilst non-depressed individuals preferentially encode positive information, those with depression tend not to show this bias (I. H. Gotlib et al., 2011). These factors may represent reasons why the significant associations between positive life events and cognitive biases and their components were not influenced by anxiety and depression symptoms, whilst those regarding negative life events were.

The impact of psychopathology across the primary genetic analysis demonstrated that the significance of the CSS as moderating negative life events on non-social interpretation bias was confounded by the presence of depression and anxiety symptoms. This likely suggests that the initial significant finding was in part a result of these existing depression and anxiety symptoms, and possibly that the effects of negative life events as moderated by the CSS on non-social interpretation bias are more dependent on depression and anxiety status. However, despite a lack of robustness here, all other significant interactions and direct associations involving the CSS held when controlling for depression and anxiety, with little change in effect size or significance.

Across the secondary analysis, the significant associations between memory bias and CNR1 (rs1049353) and CRHR1 (rs110402), were both found to be non-significant when controlling for depression and anxiety symptoms. Past research has demonstrated moderating effects of rs1049353 and main effects of rs110402 on depression (Agrawal et al., 2012; Ishitobi et al., 2012). This could suggest that the original findings were due to a negative memory bias that developed as a result of anxiety and depression symptoms, or due to a reciprocal relationship between a negative memory bias and these psychopathologies. This hypothesis would be in keeping with previous research that has demonstrated negative biases in memory as a significant mediating component of both anxiety and depression (Raes, 2010). However, despite these associations being confounded by depression and anxiety symptoms, all other significant direct

associations and interactions regarding the candidate sensitivity variants remained significant. Furthermore, those that remained significant also showed minimal change in p-value or effect size.

Taken together, this suggests that these specific genetic variants implicated in environmental sensitivity, both cumulatively and independently moderate the effect of both positive and negative life events on the majority of cognitive biases tested irrespective of anxiety and depression symptoms. These findings are in line with previous twin studies of cognitive biases (Eley et al., 2008; Rijsdijk et al., 2009), confirming that there is a heritable component to cognitive biases. Furthermore, in line with the CogBIAS Hypothesis, these findings demonstrate that this genetic effect also moderates life events on the development of cognitive biases despite the limited main effect of life events themselves when accounting for depression and anxiety symptoms.

4.4.5. Limitations

One key limitation of the current study is the absence of attention bias, as it represents the most heavily assessed cognitive bias with past research demonstrating its associations with both behavioural traits and psychopathologies. There were particular concerns regarding the dot probe task used to measure participants' attention bias. For example, analysis revealed that the model fit for attention bias was non-significant for all fixed or random effects of time and life events. Reliability analysis revealed that this was likely due to the dot probe task lacking internal consistency leading to non-significant correlations over time, and consequently to attention bias being dropped from all further analysis. Attention bias scores are often derived from reaction times in the dot probe task, as they were in the current study. However, recent research examining the psychometric properties of reaction time indices of attention bias have shown that they have poor split-half and retest reliability (H. Brown et al., 2014; Kappenman, Farrens, Luck, & Proudfit, 2014; Kappenman, MacNamara, & Proudfit, 2014; Price et al., 2015a; Schmukle, 2005; Staugaard, 2009). Researchers have suggested that a key limitation of the dot-probe task is that it lacks the precision to be able to differentiate between "initial orienting" and "subsequent disengagement" (Grafton & MacLeod, 2014; Grafton, Watkins, & MacLeod, 2012). This is a result of the task only assessing attention at the time the dot appears, which constitute a single time point. Before the dot appears on the screen, participants are free to switch their attention between the two stimuli as many times as they please. This negatively impacts on both the sensitivity and validity of the dot-probe task to assess the varying components of attention. Whilst a variety of computer-based tasks

are being used in an attempt to address the limitations of the dot-probe tasks (Grafton, Southworth, Watkins, & MacLeod, 2016; Koster et al., 2005; Rinck & Becker, 2005), one approach that has shown particular promise is the use of eye-tracking software, which will be discussed in further depth in Chapter 6 (**Section 6.5**).

A further limitation is that the current study took a candidate gene approach which brings with it many caveats. For example, the candidate gene approach requires a strong biological hypothesis in order to select appropriate candidates, but knowledge regarding the specific biological mechanisms underlying behavioural traits and psychiatric disorders is often limited. This coupled with publication bias for research demonstrating significant novel effects over null or negative replication efforts (Bosker et al., 2011; Collins et al., 2012), suggests that candidate gene findings might not be very robust. This potentially reduces the reliability of the genetic variants selected for the current study. Similarly, with a number of contradictive results between studies regarding both the direction of effect of specific genetic variants' alleles, and indeed which allele, or whether either allele represents a 'sensitivity' allele, it is possible that in some cases, both variant selection and subsequent allele coding may have been incorrect. This again, is an inherent problem with the candidate gene approach. Furthermore, and representing a more fundamental issue, it is well established that the genetic architecture of common behavioural traits is highly complex and polygenic (Donnelly, 2008), influenced by many thousands of variants of small effects rather than by a few variants of large effect (Culverhouse et al., 2018). Therefore, a genome-wide approach may prove to be more reliable and promising (see Chapter 5).

Another limitation was that the relatively small sample size of the current study may have impacted on results, especially when assessing the effect of minor allele homozygotes including rs25531 (0), rs6314 (1), rs5522 (3), rs1799971 (6), and rs6265 (16). As in the case of rs6265, which was the most consistently significant finding, there were only 16 participants in the current study who were homozygote for the minor allele. This resulted in very wide confidence intervals and no significant difference between heterozygotes (TC) and minor allele homozygotes (TT). This, and the low number of minor allele homozygotes also led to these genotypes being collapsed and assessed together in further simple slope analysis examining. Furthermore, there were also no significant main effects of the minor allele homozygotes (TT) on cognitive biases following multiple testing corrections, suggesting that the significant interactions regarding rs6265 may have been driven by results regarding the TC carriers of rs6265. However, it is also possible that the

low number of homozygote T-allele carriers in the current study, and the consequent wide confidence intervals, resulted in non-significant associations that were likely having significant effects. Therefore, it is thought that with a larger sample size the true differences between these genotypes would become more evident.

Finally, the measure of positive and negative life events was recorded using CASE, a self-report retrospective questionnaire which asks participants to indicate whether they have experienced particular events over the last year and rate them as positive or negative on a 6-point Likert scale. Whilst an in-depth interview paradigm, such as the *Life Events and Difficulties Schedule* (LEDS) (Brown and Harris, 1978), may be a more accepted method of collecting life event data, checklist questionnaires offer a much more cost effective, and less time-consuming way of obtaining such data across large samples. However, whilst such methods allow for larger projects to collect data that would otherwise not be possible, they also come with inherent limitations. For instance, although the CASE questionnaire addresses both the occurrence and severity of 38 items and allows for two life events not present in the list, it is reasonable to suggest that some participants may have experienced multiple occurrences of a single life event. Whilst participants reporting life events in the CASE questionnaire can only indicate that a life events has occurred, a LEDS interview is sensitive to the frequency of such events. Other issues, including recall bias and mood congruency effects, are also evident when using self-report retrospective questionnaires such as CASE. Inaccurate recall, the mood of the participant upon filling out the questionnaire, as well as their current cognitive biases may have impacted on the severity given for the events reported. Whilst sensitivity analysis was conducted to examine the robustness of the significant associations the resulting reduction in power, due to the removal of over half the items from the CASE list of events, likely rendered the study underpowered to detect other valid and significant effect. As in-depth interviews tend not to be viable for such large-scale studies, future research in this area should consider using life event inventories whereby each item has been pre-assessed for severity and carry a pre-assigned weight. This will help assure that responses are not confounded by participants' interpretations of the items, which may be driven by the behavioural trait that is being assessed (i.e., cognitive biases). Future studies should also consider collecting more objective and prospective data, rather than relying on retrospective questionnaires, as this would avoid the caveats of recall bias and mood congruency effects mentioned above as well as other confounding factors.

4.4.6. Implications

Notwithstanding the above limitations, these findings could have important implications for research and in the prevention and treatment of psychiatric disorders. For example, in terms of implications for research, the current study has demonstrated the importance of examining both genes and the environment when assessing the development of cognitive biases. However, it has also been shown that positive as well as negative environmental effects should be considered when assessing the development of cognitive biases (both positive and negative). Additionally, as the association of these positive and negative life events differed, with respect to whether they were dependant or independent of an individual's behaviour, it becomes clear that the nature of the life events must be considered if attempting to assess potential causal mechanisms of these biases.

Sensitivity analysis also revealed that whilst the associations regarding positive life events remained robust to the effects of depression and anxiety, with little change in effect size, the same was not the case for the associations regarding negative life events. The associations between negative life events and cognitive biases and their components were, in all but one case (negative component of memory bias), significantly driven by depression and anxiety symptoms. This suggests that the association of positive life events with the development of positive cognitive biases operate independently to current psychopathology, whilst the those of negative life events on negative cognitive biases are considerably more dependent on depression and anxiety status. This clearly highlights differences in the dimensional structure of positive and negative biases, and the need for further research into these distinct developmental differences.

Whilst the current chapter has demonstrated that variants implicated in previous GxE studies of depression and anxiety are associated, both cumulatively and individually, with variations in the development of cognitive biases, several novel findings were also demonstrated. Specifically, it has been shown that a lack of positive life events and an absence of positive bias components may be important factors in the development of negative biases. For example, the interaction between the CSS and positive life events on memory bias demonstrated, even when controlling for depression and anxiety, that a lack of positive life events was associated with a more negative memory bias, despite being found in the low CSS group. This suggests that those in the low CSS group develop a more negative memory bias, which was interestingly driven by a lack of the positive component of memory bias (*positive memory bias*), in the absence of positive

environments. However, this finding is also in direct opposition to the assumptions provided by both the Differential Susceptibility Hypothesis and CogBIAS Hypothesis, and therefore requires more investigation. Additionally, the significant direct association between the CSS and an increased negative social interpretation bias, after controlling for depression and anxiety, was driven by a lack of its positive component (*positive social interpretation bias*). Taken together, these findings, if replicated would suggest firstly, that the GxE interactions on cognitive biases may not operate according to the framework of Differential Susceptibility, and secondly, that the absence of a positive bias component, rather than the presence of a negative bias component, may be genetically driven and of great importance for the development of negative cognitive biases. However, more research is required as this is the first time such associations have been observed. If replicated these findings may also have important implication for the prevention of disorders such as depression and anxiety, as these biases may represent intermediate phenotypes for such psychopathologies. For instance, those at risk could potentially be identified based on their genotype, and strategies could then be put in place to develop a more positive bias and reduce or prevent the development of a negative bias, providing a protective effect against later psychopathology. Furthermore, as the assessment of the current sample was conducted during a particularly sensitive periods in participants' development, this could represent an important time to target those individuals at risk and put in place prevention strategies to stop a negative cognitive bias from establishing and lessen the likelihood of later psychopathology.

4.4.7. Conclusion and Future Directions

The present study has confirmed findings from previous research concerning an overlap between genetic variants implicated to increase sensitivity to environmental effect in GxE research of depression and anxiety, and cognitive biases in memory and interpretation. Furthermore, by highlighting both direct associations and moderating effects of the CSS by positive life events on memory bias, the study has confirmed the majority of hypotheses, providing support for part of the CogBIAS Hypothesis, with some exceptions. However, overall results suggest that variations in genotype do have a significant impact on the development of cognitive biases, supporting both the CogBIAS model and the majority of the current study's hypotheses. Replication in an independent sample with similar, or preferably better measures of the environment and cognitive biases and assessing the same genetic variants is required to assess the validity and reliability of

these findings. However, moving forward it is essential that the specific limitations highlighted above are addressed. What is needed is more prospective studies and/or accurate, weighted measures of objectively assessed positive and negative life events, the use of eye tracking software to reliably measure attention bias, and a much larger sample size so as to have enough power to detect the effect of all genotypes, especially homozygote minor alleles.

As a next step, a whole-genome hypothesis free exploration of cognitive biases should be applied, with the use of polygenic risk scores to assess specific phenotypic associations. From here it will be possible to identify phenotypes associated with cognitive biases, using a phenome-wide approach and based on that approach, assess whether these cognitive biases could mediate the relationship between genetic risk for psychopathology such as depression and anxiety and later outcomes. This approach could ultimately highlight cognitive biases as intermediate phenotypes for psychopathologies and provide new targets for the treatment and prevention of psychiatric disorders. Furthermore, this approach would allow for the assessment of how cognitive biases might mediate the specific relationship between environmental effects and genetic risk for psychopathology and resilience set down by the CogBIAS Hypothesis.

5. Chapter 5 – Cognitive biases as potential mechanisms mediating genetic risk for depression and anxiety: A phenome-wide polygenic approach.

5.1. Introduction

As Chapter 4 demonstrated, candidate 'sensitivity' variants previously implicated in GxE research of depression and anxiety also show associations with cognitive biases in memory and interpretation providing some support for the CogBIAS hypothesis. However, to what extent these biases might mediate the relationship between genetic risk for depression and an outcome of psychopathology requires further study. Extending on the previous chapter, the current chapter aims to further test the CogBIAS hypothesis in the CogBIAS-L-S sample using a whole-genome polygenic approach. The following chapter will,

1) Assess phenome-wide associations between a publicly available polygenic score (PRS) for major depression (MDD), cognitive biases in interpretation and memory, and depression and anxiety scores both across time and by-time,
2) Examine phenome-wide associations between the MDD PRS, cognitive biases and depression and anxiety symptoms specific to each of the three timepoints,
3) Assess variance in cognitive biases and both depression and anxiety score explained by the MDD PRS and,
4) Conduct mediation analysis between time points to examine these cognitive biases as potential mediators of genetic risk on later depression and anxiety symptoms.

5.1.1. Genetic risk for depression and anxiety during development

As highlighted in Chapter 1 (**Section 1.1)**, depression and anxiety amongst children, adolescents and adults are significantly influenced by genetic factors (Boomsma et al., 2005; Edelbrock et al., 1995; Eley & Stevenson, 1999; K. S. Kendler et al., 1986; Mackinnon et al., 1990; Rice et al., 2002; Thapar & McGuffin, 1994; Topolski et al., 1997). However, due to the majority of these, being cross-sectional in design, little is known about whether genes influencing adult depression are the same as those influencing depression in childhood. This is particularly true for important developmental periods such as childhood and adolescence where there is considerable change in the expression of anxiety and depression symptoms, as well as the prevalence of anxiety and other mood disorders (Angold & Costello, 2006; Costello, Egger, & Angold, 2005; Twenge

& Nolen-Hoeksema, 2002). Understanding these changes in genetic risk for symptoms of depression and anxiety, through these developmentally sensitive periods, could have important implications for research, treatments and interventions.

There is evidence from several longitudinal twin studies that genetic effects on depression contribute to both symptom stability as well as changes over time from adolescence to early adulthood (Lau & Eley, 2006; O'Connor, Neiderhiser, Reiss, Hetherington, & Plomin, 1998; Scourfield et al., 2003; J. Silberg et al., 1999). In keeping with these findings, others have noted both innovation, and attenuation of genetic effects on both depression and anxiety throughout developmental periods of up to seven years (K. Kendler et al., 2008; Waszczuk et al., 2016). These widely supported findings, discussed in detail in Chapter 1 (**Section 1.1**), suggest that whilst early genetic effects on both depression and anxiety do dissipate (attenuation), new genetic effects also come online (innovation) leading to a stable genetic effect and the continuation of symptoms across time. However, despite the importance of longitudinal twin studies such as these, and their implications for molecular genetic research, longitudinal molecular genetic studies are limited, with previous research initially focusing on cross-sectional assessments of a small number of candidate genetic variants (Christiansen et al., 2007; Craddock et al., 2006; Frustaci et al., 2008; Verhagen et al., 2010; N. R. Wray et al., 2008). Furthermore, due to the nature of cross-sectional research these studies were unable to imply a direction of detected effects, with findings often failing to replicate in subsequent studies, bringing into question the reliability of the candidate gene approach. Given the limitations of cross-sectional molecular genetic research examining these effects, and the need to examine such effects longitudinally, an approach which utilises polygenic risk scores (PRS) tested in independent longitudinal datasets may provide a novel way of addressing this issue.

5.1.2. Polygenic approaches to depression and anxiety

As discussed in Chapter 1 (**Section 1.1.2**), genome-wide association studies (GWAS) have made some progress in identifying specific genetic variants associated with both depression (Howard et al., 2019; N. R. Wray et al., 2018) and anxiety (Purves et al., 2017). However, even the collective effects of these variants tend to explain only a minimal proportion of the heritability observed in studies using quantitative genetic methods. As discussed in detail in chapter 1 (**Section 1.1.2**), the use of polygenic approaches have shown genetic effects closer to the heritability

estimates found in twin studies (Okbay et al., 2016; N. R. Wray et al., 2018), and have also demonstrated the shared genetic architecture of phenotypes including depression and anxiety (Okbay et al., 2016). Furthermore, research has shown how a previously defined PRS for depression can predict variance in both depression *and* anxiety (Demirkan et al., 2011), lending further support to the notion of a shared genetic architecture between the two psychopathologies. However, studies such as this tend to be cross-sectional in design and more commonly examine psychopathologies in adult and elderly samples inferring stable genetic effects overtime based on limited changes in variance explained between adult and elderly samples.

More recent longitudinal studies have demonstrated several cross-phenotype associations in children using a single PRS for schizophrenia to explain variances in both depression and anxiety, highlighting heterotypic continuity between these separate childhood and adult psychopathologies (H. J. Jones et al., 2016; M. G. Nivard et al., 2017). These findings could suggest that such childhood psychopathologies precede and possibly mediate the development of distinct and likely more severe disorders later in life. However, thus far this approach is yet to be implemented to assess the developmental trajectory of common complex disorders such as depression and anxiety and examine possible phenotypic precursors, such as cognitive biases, that may represent mechanisms through which genetic risk becomes psychopathology.

To date no research has examined whether adulthood polygenic risk scores for depression predict depressive symptoms in children and adolescents, or whether the effect of such a polygenic risk score changes over time using a longitudinal design. Furthermore, whilst it is known that polygenic risk scores can predict depression and anxiety, it is still somewhat unknown through what mechanism genetic risk leads to an outcome of either psychopathology. Whilst some studies have shown that a PRS for one disorder can predict other distinct phenotypes, no study to date has, for example examined the relationship between PRS for depression or anxiety and cognitive biases. Shared genetic architectures between specific phenotypes could suggest that an onset of one could act as a developmental precursor to another, and that this could mediate the development of a separate psychopathology later in life.

5.1.3. Cognitive biases as mediators of genetic effects on depression and anxiety

As discussed in Chapter 1 (**Section 1.2.2**) cognitive biases in attention, interpretation and memory have been suggested as potential mechanisms for the development and maintenance of both depression and anxiety (Bar-Haim et al., 2007; Ian Gotlib et al., 2004; I. H. Gotlib & Joormann, 2010; Joormann & Gotlib, 2010; Mathews & MacLeod, 2005b). Findings from a longitudinal twin study by Lau and Eley (2008) have also demonstrated a reciprocal relationship between attribution style and depression using a cross-lagged mediation model. However, issues regarding cause and effect remained, as the chronicity of their appearance was difficult to disentangle due to the need for earlier measures of both outcome and mediator. Other twin studies assessing the impact of cognitive biases such as anxiety sensitivity on depression and anxiety (Zavos, Rijsdijk, et al., 2012) and panic/somatic ratings (Eley et al., 2007) in children and adolescents have demonstrated significant associations overtime, and genetic overlap respectively. However, these studies were unable to assess any potential mediating effects.

Whilst still somewhat limited, research using genome-wide data has begun to assess mediators of polygenic risk for affective disorders such as depression, using related phenotypes such as neuroticism and resilience (Navrady et al., 2018). However, again, such approaches are yet to examine the potential mediating role of cognitive biases in the development of affective disorders.

The research presented above suggests a distinct need for further assessment into the possible mediating effects of cognitive biases in the relationship between genetic risk and psychopathologies such as depression and anxiety. Whilst several twin studies have suggested the need for research assessing cognitive biases as a potential mechanism mediating genetic risk on psychopathology, very little research to date has attempted to address this, especially using genome-wide data and phenotypic measures across multiple timepoints. Therefore, given a relatively wide range of phenotypes assessed at three time-points, and with the inclusion of genome-wide data, the CogBIAS-L-S (Booth et al., 2017) provides an ideal dataset to test this hypothesis.

5.1.4. Aims and hypothesis

The aim of the current study is to use the CogBIAS-L-S sample of healthy adolescents to further test the CogBIAS hypothesis using a publicly available genome-wide adult major depression PRS (MDD PRS) (N. R. Wray et al., 2018), obtained from the psychiatric genomics consortium (see http://pgc.unc.edu). An MDD PRS was chosen as previous research has demonstrated that such a PRS can predict variance in both depression and anxiety and therefore represents the most relevant PRS in term of the outcomes of interest in the current study. Furthermore, due to the limited sample size, and in order to avoid further stringent multiple testing corrections, only a single PRS was assessed in the current study.

Phenome-wide associations between genetic risk for depression (MDD PRS) and cognitive biases in interpretation and memory, their positive and negative components, and self-reported symptoms of depression and anxiety will be assessed across all time points. Attention bias will not be included in the analysis as it was found to have poor reliability when assessed in the previous chapter. These exploratory analyses are expected to demonstrate associations between genetic risk for depression (i.e., MDD PRS) and self-reported depression and anxiety symptoms within the CogBIAS-L-S sample, as measured by the Revised Children's Anxiety and Depression Scale - Short Form (RCADS-SF). This is also expected to extend to cognitive biases, with the MDD PRS also showing associations with interpretation and memory biases, as well as their positive and negative components, at multiple *p*-value thresholds. However, the magnitudes of these associations are not expected to be the same across the biases and components tested due to the different measures used and the unlikeliness of full correlation between the bias scores. Furthermore, it is thought that associations between the MDD PRS and cognitive biases will be specific to a select number of *p*-value thresholds. This is likely, as with the introduction of more variants comes a greater likelihood of creating more statistical noise as a result of introducing variants with no association with the cognitive biases.

The effect of PRS-by-time interactions on both cognitive biases, including their positive and negative components, as well as self-reported depression and anxiety scores will also be examined. This interaction analysis will show whether the effects of the PRS are stable over time, or whether it changes throughout the three time points. It is expected that there will be little to no significant interactions between the PRS and time on either psychopathology (depression and

anxiety), or cognitive biases. However, any significant findings will be examined further using simple slope analysis, with margin plots to illustrate these effects further.

To further probe these relationships, cross-sectional associations between the MDD PRS, the cognitive biases, including their positive and negative components, and depression and anxiety symptoms will be assessed at each wave. This analysis will allow for associations specific to each wave to be assessed in greater detail. Here, it is expected that there will be significant associations between the MDD PRS and depression and anxiety as well as the cognitive biases, including their positive and negative components. This is expected across all three waves and at multiple *p*-value thresholds.

Following this, variance in all assessed phenotypes explained by the MDD PRS at each wave across three incremental *p*-value thresholds will be assessed. This will be examined in both the full sample and in only those that were present at all three waves of data collection. This further exploratory analysis is expected to reveal the effect of dropouts on associations between the MDD PRS, cognitive bias and psychopathology phenotypes across the three waves. Survival analysis will also be conducted to assess differences in dropout rates in those with high and low polygenic scores.

Following the above exploratory analysis, mediation analysis will be conducted. These analyses will be informed by the previous analyses regarding the effects of the MDD PRS on depression and anxiety, and each of the cognitive biases. In these analyses' significant associations between the MDD PRS at specific *p*-value thresholds, psychopathologies and any of the significantly associated cognitive biases will be assessed to ascertain whether these cognitive biases mediate the relationship between the MDD PRS and self-reported depression and anxiety. Depending on the outcome of the exploratory analysis, the mediation analysis will examine whether cognitive biases mediate this relationship between each wave (wave 1–wave 2, and wave 2–wave 3), and across all waves (wave 1–wave 3). As cognitive biases have been implicated as potential intermediate phenotypes for psychopathology, and providing exploratory analysis identifies adequate associations, it is expected that the cognitive biases will significantly mediate genetic risk for depression on symptoms on psychopathology at later waves.

5.2. Methods

5.2.1. Sample

The current study used the same data from the same CogBIAS-L-S as was used for the previous chapter. The sample itself, including information regarding the recruitment process and inclusion criteria is described in greater detail in Chapter 2 (**Section 2.2.2**). Briefly, the original sample consisted of 504 11-12-year-olds (226 males, 278 females) at the initial data collection stage (wave 1). However, the final number of participants across each wave, following quality control and population stratification (Europeans only), were as follows: 391 (191 males and 200 females) 11-12-year-olds at wave 1, 349 (167 males and 182 females) 14-year olds at wave 2, and 323 (146 males and 177 females) 16-year olds at wave 3.

5.2.2. Measures

The same measures used in Chapter 4, regarding cognitive biases in interpretation (*The Adolescent Interpretation and Belief Questionnaire* (AIBQ)) and memory (*The Self-Referential Encoding Task* (SRET)) were also used in the current chapter. This was also the case for measures of psychopathologies depression and anxiety (*Revised Children's Anxiety and Depression Scale - Short Form* (RCADS-SF)). These measures are described in detail in Chapter 2 (**Section 2.2.4**).

Unique to this chapter is the use of an MDD PRS that was created from the summary statistics of a large scale GWAS meta-analysis of major depression (N. R. Wray et al., 2018), and included a total of 9,884,712 variants. These variants were used to created PRS for each participant, with variants included at different *p*-value threshold, based on their availability within the sample, ranging from 8,173 to 114,860. This MDD PRS was used to assess genetic overlap, and variance explained for cognitive biases, their positive and negative components and self-reported measures of depression and anxiety within the CogBIAS-L-S sample. The MDD PRS was also used across all mediation analysis as an independent variable. Further information regarding the MDD PRS used in the current study is presented in Chapter 2 (**Section 2.3.3.4**).

5.2.3. Procedure

Testing regarding the cognitive bias, life experience and mental health was conducted at the participants' school with participants split into small groups and completing two separate test sessions. However, in some cases it was necessary for participants to complete testing at the Department of Experimental Psychology, University of Oxford. Further, in depth details regarding the testing procedure can be found in Chapter 2 (**Section 2.2.3**) and *"The CogBIAS longitudinal study protocol. Cognitive and genetic factors influencing psychological functioning in adolescence"* (Booth et al., 2017).

5.2.4. Genotyping

Participants provided saliva sample using DNA Genotek Oragene OG-500 collection kits. DNA extraction was performed, and genotyping conducted using the Illumina Human Omni express-24 chip. For more detailed information regarding the genotyping and imputation relevant to study three (Chapter five) please see Chapter 2 (**Section 2.2.5**).

5.2.5. Statistical Analysis

Firstly, phenome-wide analysis was conducted to assess the relationship between the MDD PRS and all cognitive biases under examination, including their positive and negative components. To do this linear mixture models were constructed in accordance with analysis from the previous chapter. The MDD PRS was included as a fixed effect, with time as both a random and fixed effect in order to assess whether the cognitive biases, and their positive and negative component changed significantly across the three waves. This analysis was also conducted to assess the relationship between the MDD PRS and depression and anxiety scores separately. All models were assessed at multiple *p*-value thresholds of the MDD PRS across all waves. MDD PRS-by-time interactions were also included in the above model in order to examine whether the associations between the MDD PRS and cognitive biases varied across time. These models were then rerun examining the relationship between the MDD PRS and depression and anxiety scores individually, within the CogBIAS sample.

Following this, regression analyses, with identical parameters as in the above models were performed to assess associations between the MDD PRS and all cognitive biases under

examination, including their positive and negative components at each wave. Like before these models were also run to assess the relationship between the MDD PRS and depression and anxiety scores separately. Next, all cognitive biases, their components, and psychopathologies within the CogBIAS sample were assessed in terms of variance explained by the MDD PRS, examining both the full sample and only those present at every wave of data collection. Survival analysis was also conducted to assess the extent of dropouts across the three waves in those with high and low PRS as defined by median split.

Having established associations between the MDD PRS, cognitive biases, their positive and negative components, and self-reported depression and anxiety symptoms, mediation analysis was conducted. This analysis was run across those *p*-value thresholds with the greatest significance and variance explained in the previous models. The simple mediation analyses assessed the association between the MDD PRS (independent variable) on wave two psychopathology (dependent variable) mediated by cognitive biases (mediator variable) at wave one, on wave three psychopathology mediated by cognitive biases at wave two, and on wave three psychopathology mediated by cognitive biases at wave one. The most significant findings were then assessed in greater detail, with inverse relationships between the mediator variable and dependant variable examined to assess potential reverse causality.

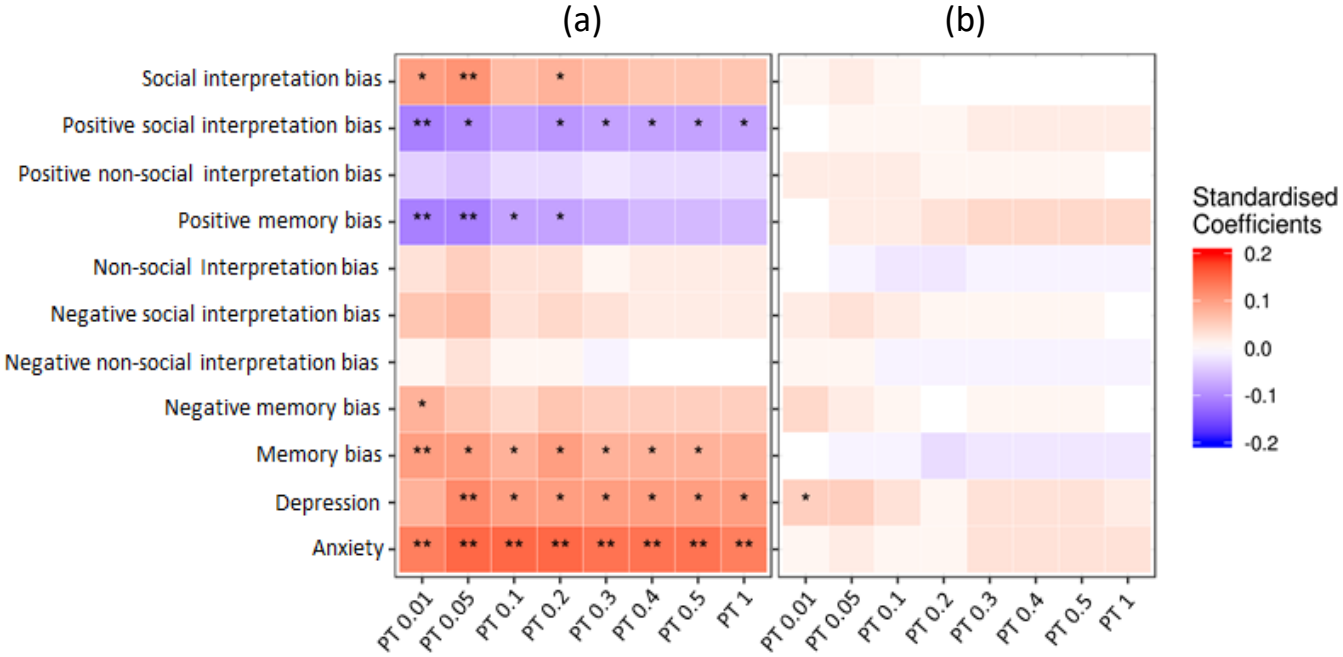
As with the previous chapter the inclusion of both age and sex as fixed effect covariates was implemented across all analysis. Additionally, ten principal components were regressed against the MDD PRS at each threshold creating a residual PRS to control for population stratification. Results and commentary regarding these analyses can be found in the **appendix (vi).** Regression analysis regarding the principal components was performed using PRSICE v1.25 (Euesden, Lewis, & O'Reilly, 2015). All other analyses, including the descriptive statistics, the main effect of the PRS across time and by-time interactions and mediation analysis were conducted using STATA 12.1 (StataCorp, 2011).

5.3. Results

5.3.1. The effects of the MDD PRS across all waves and by-time interactions on cognitive biases and psychopathology.

Mixture models were constructed to the same specification as those constructed in the previous chapter, and as described in the method section above. A total of eight *p*-value thresholds were examined (0.01, 0.05, 0.1, 0.2. 0.3, 0.4, 0.5, 1) across each of the cognitive biases, their positive and negative components, and psychopathologies depression and anxiety. The results regarding the effects of the MDD PRS across time and the MDD PRS-by-time interactions on each of the these phenotypes is presented in the heatmap below (**Figure 5.1**).

Figure 5.1. Displaying the associations between the psychiatric genomic consortiums' 2018 MDD PRS, cognitive biases and their positive and negative components, as well as depression and anxiety measures across time (a) and by time (b) within the CogBIAS longitudinal study.



Note: Each heatmap displays eight p-value threshold (PT) ranging from 0.01 – 1 for each of the biases and their components, as well as the psychopathologies depression and anxiety. The colours within the heatmap represent the direction of effect as defined by the standardised beta coefficients. A single asterisk **('*')** indicates a p-value that was significant prior to multiple testing corrections, whilst a double asterisk **('**')** indicates those significant following correction for multiple testing.

The heatmap above (**Figure 5.1**) demonstrates that self-reported anxiety and depression scores had consistent positive associations with the MDD PRS, suggesting that the effect of the MDD PRS is associated with higher anxiety and depression scores across the three waves, with anxiety showing the strongest association with the MDD PRS. The MDD PRS was shown as having a significant positive association with anxiety scores following correction for multiple testing across all *p*-value thresholds. In contrast, this association was only found to survive multiple testing correction at a single threshold for depression (PT 0.05), and was only nominally significant across the remaining threshold, with the lowest threshold (PT 0.01) found to be non-significant. This may possibly be due to the samples young age, and anxiety being a potential precursor to later depression.

The MDD PRS was also associated with several of the cognitive biases across the three waves. There were significant associations between the MDD PRS and memory bias as well as social interpretation bias across the three time points. For memory bias there was a significant positive association, thereby increasing a negative memory bias across all *p*-value thresholds with the exception of one threshold (PT 1) which was non-significant. Furthermore, this association survived correction for multiple testing at the lowest threshold (PT 0.01). Similarly, social interpretation bias was also shown to have a significant positive association with the MDD PRS increasing a negative bias in the interpretation of social scenarios. However, this association was somewhat inconsistent, as whilst one association did survive multiple testing correction (PT 0.05), only two additional thresholds were found to be nominally significant (PT 0.01 and PT 0.2). For the positive and negative components of each of these biases only *positive social interpretation bias* and *positive memory bias* showed any consistent associations. A nominal association was also highlighted for the negative component of memory bias (*negative memory bias*), however this was only at a single threshold (PT 0.01) and may therefore be a spurious finding. For *positive social interpretation bias* there were negative nominally significant associations found across all threshold with one exception (PT 0.1). Additionally, the lowest threshold (PT 0.01) of the MDD PRS was found to have a significant negative association with *positive social interpretation bias* following multiple testing correction, implying that the MDD PRS is significantly associated with reduced positive interpretation of social scenarios at the threshold. The positive memory bias component (*positive memory bias*) had a negative association with the MDD PRS, suggesting that the MDD PRS is associated with a reduction of the number of positive words endorsed and recalled

in the SRET task. This association was found to be significant following multiple testing correction at two p-value thresholds (PT 0.01 and PT 0.05), and nominally so at two further thresholds (PT 0.1 and PT 0.2).

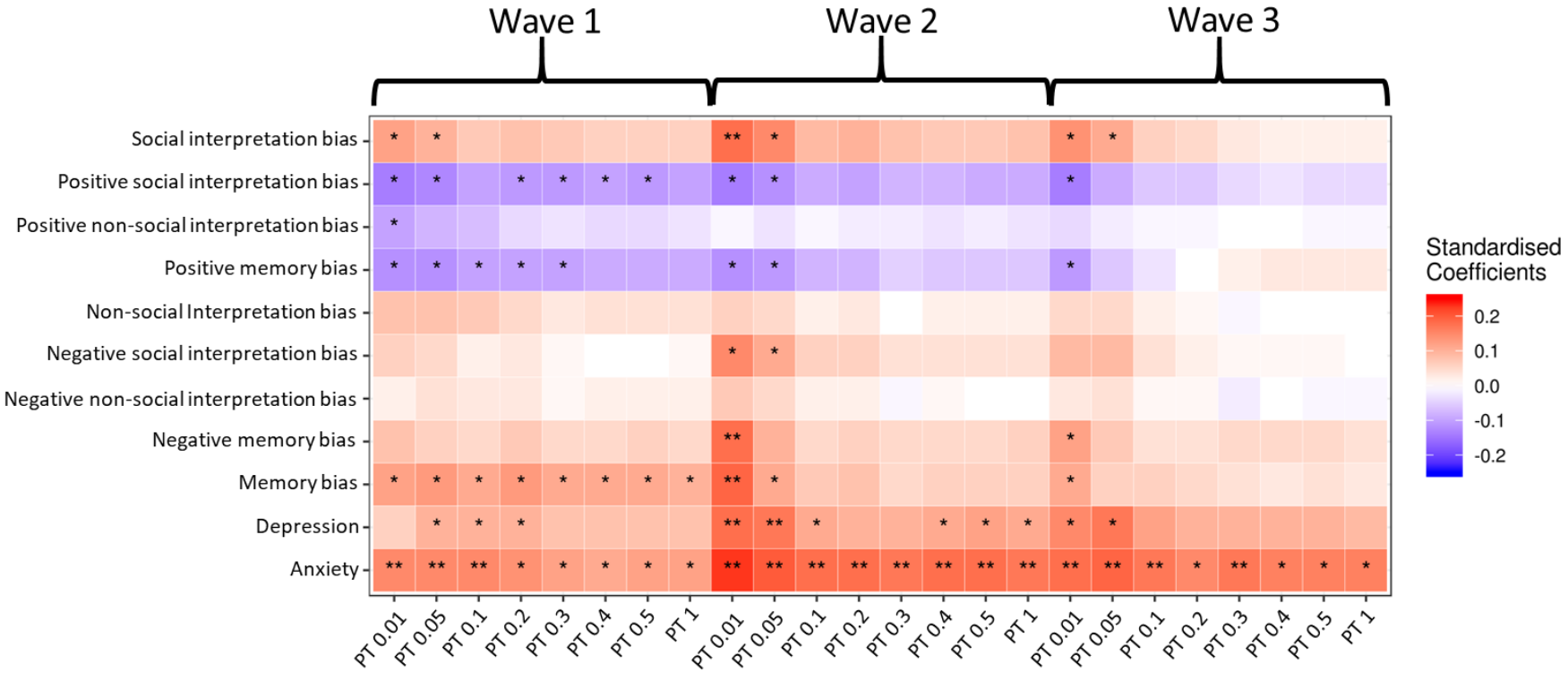
For the MDD PRS-by-time interaction analysis there was a complete lack of any significant findings across all of the cognitive biases and their positive and negative components suggests that the effects of the MDD PRS on these biases and their components are stable across the three waves. For the PRS-by-time interaction analysis on both depression and anxiety, only depression showed a significant positive association, suggesting that the effects of the MDD PRS increases depression scores across the three waves. However, this association did not survive correction for multiple testing and was confined to a single threshold (PT 0.01). Despite this, simple slope analysis was conducted to examine this interaction in more depth. In these analyses, the linear effects of the MDD PRS (PT 0.01) were tested separately at each wave.

These analyses revealed a non-significant positive association between the MDD PRS and depression score at wave one (β=.03, 95%CI=-0.06-0.12, *p*=.478), followed by a significant positive association at waves two (β=.14, 95%CI=0.03-0.24, *p*=.010) and a non-significance positive association at wave three (β=.11, 95%CI=-0.00-0.22, *p*=.060). The results of this analysis suggest that the positive association between the MDD PRS and depression scores does significantly increase from wave 1 to wave 2, suggesting increasing depression scores over this time period in association with the MDD PRS (PT 0.01). However, and possibly due to a drop in sample size, whilst there is still a comparable positive direction of effect at wave three the association did not reach statistical significance.

5.3.2. MDD PRS main effects at each wave.

To further explore the main effect of the MDD PRS on depression and anxiety, as well as cognitive biases in interpretation and memory, including their positive and negative components at each wave, regression analysis was performed. The MDD PRS was regressed across each wave separately for depression and anxiety scores, social and non-social interpretation bias, and memory bias, as well as their positive and negative components. The results are illustrated in the heatmap in **Figure 5.2**.

Figure 5.2. Displaying the associations between the psychiatric genomic consortiums' 2018 MDD PRS, cognitive biases and their positive and negative components, as well as depression and anxiety measures at each of the three waves of the CogBIAS longitudinal study.



Note: Each wave displays eight p-value threshold (PT) ranging from 0.01 – 1 for each of the biases and their components, as well as the psychopathologies depression and anxiety. The colours within the heatmap represent the direction of effect as defined by the standardised beta coefficients. A single asterisk ('*') indicates a p-value that was significant prior to multiple testing corrections, whilst a double asterisk ('**') indicates those significant following correction for multiple testing.

In **Figure 5.2** it can be clearly seen again that the MDD PRS predicts anxiety, more consistently and to greater significance than depression. However, in both cases the direction of effect was in the expected direction with the MDD PRS positively associated with depression and anxiety scores. The MDD PRS was significant at all waves and at all thresholds prior to multiple testing correction for anxiety within the CogBIAS-L-S sample. Of these, three thresholds remained significant following multiple testing correction at waves 1 (PT 0.01, PT 0.05 and PT 0.1), whilst four remained so at wave 3 (PT 0.01, PT 0.05, PT 0.1 and PT 0.03), with all thresholds shown to be significant following multiple testing corrections at wave 2. This consistent positive association suggests that the effect of the MDD PRS, at multiple thresholds, is consistently associated with increased anxiety scores at each of the three waves.

In contrast, there were only two associations between the MDD PRS and depression within the CogBIAS sample that survived multiple testing correction, both of which were at the two lowest thresholds at wave 2 (PT 0.01 and PT 0.05). Nominally significant associations between the MDD PRS and depression were also found at further thresholds at wave 2 (PT 0.1, PT 0.4, PT 0.5 and PT 1). Depression was also found to be nominally significant at three thresholds at wave 1 (PT 0.05, PT 0.1, PT 0.2), and two thresholds at wave 3 (PT 0.01 and PT 0.05). The direction of effect was in the expected direction, and in keeping with result pertaining to anxiety, with the effect of the MDD PRS shown to be associated with higher depression scores at each wave.

The pattern of association between the MDD PRS and the cognitive biases, and their positive and negative components at wave 1 highlighted several consistent nominally significant findings. The MDD PRS had consistent nominally significant positive associations with memory bias at all thresholds at wave 1, thereby suggesting that the MDD PRS is associated with an increased negative memory bias. The consistency of the findings at each threshold also gave validity to these association. The positive component of memory bias (*positive memory bias*) also showed relatively consistent nominally significant associations for the first five threshold at wave 1. However, here a negative association was observed, suggesting that the effect of the MDD PRS was associated with less positive words endorsed and recalled in the SRET task at wave 1 and therefore a reduced positive memory bias. To a lesser extent the MDD PRS also showed nominally significant associations with social interpretation bias, although only at the lowest two thresholds at wave 1. Here the MDD PRS was seen to have a positive effect on social interpretation bias thereby being associated with a greater negative bias in social interpretation. However, for the

positive component of social interpretation bias (*positive social interpretation bias*), a more consistent set of associations were observed. The MDD PRS was shown to have a negative association with positive social interpretation bias across six thresholds, highlighting the MDD PRS as associated with less positive interpretations of social scenarios. Lastly, the MDD PRS was also found to have a negative association with the positive component of non-social interpretation bias (*positive non-social interpretation*). The effect, similar to that on positive social interpretation bias, was associated with reduced positive interpretations of non-social scenarios. However, this result was only nominally significant at a single threshold (0.01), and therefore lacks consistency and may not be a valid finding.

At wave 2 a distinct drop was observed regarding the associations between the MDD PRS and all cognitive biases and their components beyond two specific thresholds (PT 0.01 and PT 0.05). However, the MDD PRS showed significant positive associations with memory bias, social interpretation bias and the negative component of memory bias (*negative memory bias*) at the 0.01 threshold, the latter of which was previously non-significant at wave 1. Furthermore, all three significant positive associations remained significant following correction for multiple testing, being significantly associated with more negative biases in social interpretation and memory bias, and increased numbers of negative words endorsed and recalled in the SRET task (*negative memory bias*) at wave 2. At the 0.05 threshold both social interpretation bias and memory bias were no longer significant following multiple testing correction, whilst the negative component of memory bias (*negative memory bias*) was no longer significant nominally or otherwise. Other nominally significant results regarding the positive components of social interpretation bias (*positive social interpretation bias*), and memory bias (*positive memory bias*), and the negative component of social interpretation bias (*negative social interpretation bias*) were also observed. These findings were nominally significant at thresholds 0.01 and 0.05 and were in the expected direction, associated with a more negative social interpretation bias, and a less positive social interpretation bias, as well as less positive words endorsed and recalled in the SRET task at wave 2.

Wave 3 saw a further drop in significance between the MDD PRS, and cognitive biases and their positive and negative components. The MDD PRS remained significant and positively associated with a more negative memory bias and the negative component of memory bias (*negative memory bias*) at wave three although neither survived correction for multiple testing,

with the association confined to a single threshold (PT 0.01). The significant association from wave two between the MDD PRS and social interpretation bias remained significant at wave three at the same two thresholds (PT 0.01, and PT 0.05), with the same positive direction of effect, thereby associated with a more negative interpretations of social scenarios. However, the association did not survive correction for multiple testing. Of the positive component, positive memory bias and positive social interpretation bias, that were nominally significant at two thresholds (PT 0.01, and PT 0.05) at wave two, both remained nominally significant at wave three albeit only at a single threshold (PT 0.01). The negative direction of effect was maintained suggesting that this association is specific to less positive words endorsed and recalled in the SRET, as well as less positive interpretations of social scenarios.

5.3.3. Variance explained by major depression PRS

The associations between MDD PRS, depression and anxiety scores, and cognitive bias in memory and interpretation, as well as their positive and negative components, were then assessed in terms of variance explained by the MDD PRS as expressed by Nagelkerke r^2. This was assessed across the two most consistently significant p-value thresholds from the previous analysis (**Table 5.1)**.

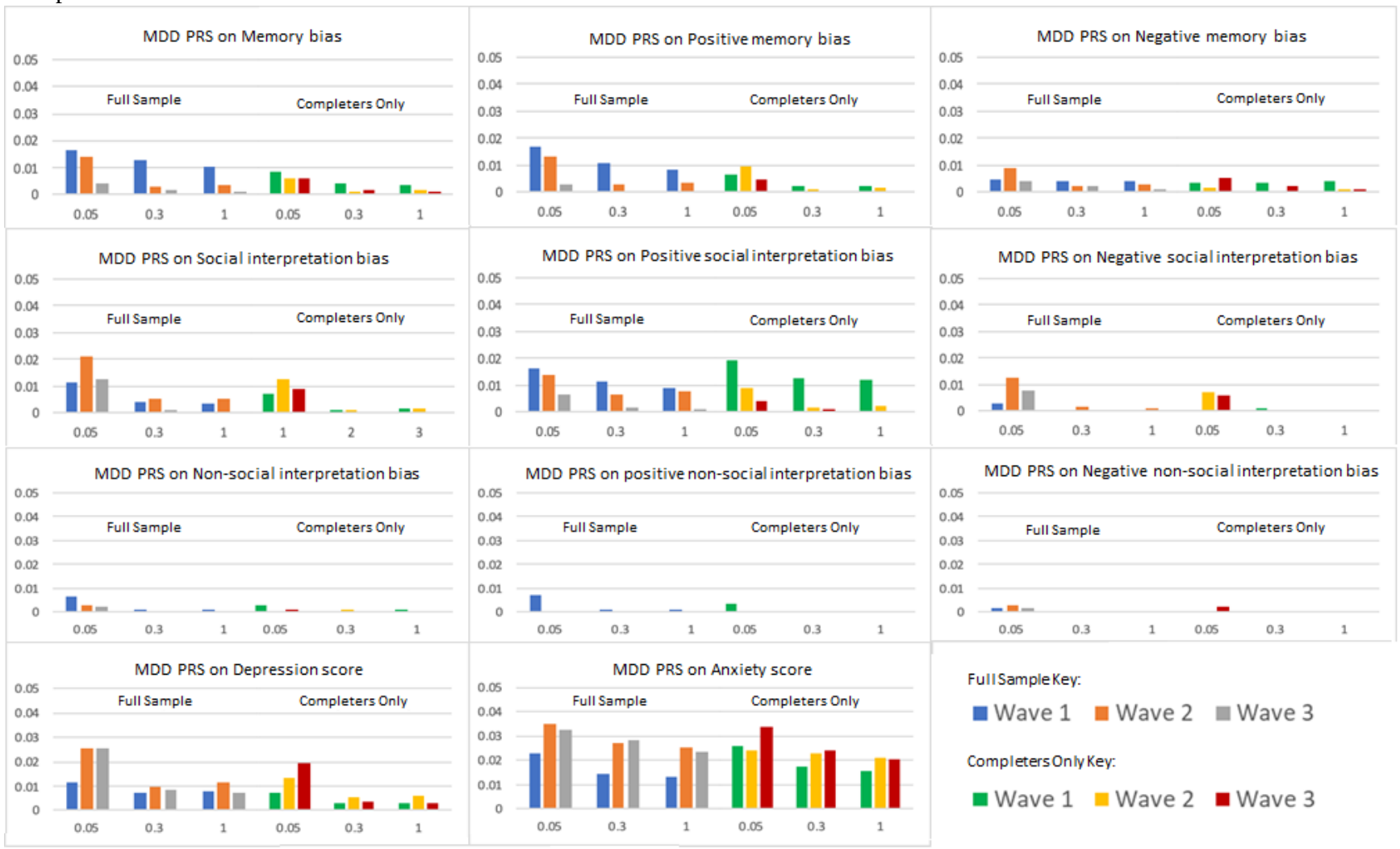
Additionally, due to the dropouts across the three waves resulting in a reduction of power to detect the variance explained at waves two and three, it was also necessary to assess whether the MDD PRS-by-time interaction detected by the mixture model in **Figure 5.1(b)** was a reliable finding, and not due to the reduction in sample size. In order to examine this, the variance explained by the MDD PRS for the cognitive biases, their positive and negative components and both depression and anxiety scores were examined both across the whole sample and for only those participants present at all waves (completers). This was examined across each wave and at three specific incremental thresholds of those previously examined (PT 0.05, PT 0.3, PT 1). Results can be found in the bar charts below (**Figure 5.3).**

Table 5.1. Results from regression analysis exploring the associations between the MDD PRS and cognitive biases in memory and interpretation, their positive and negative components and depression and anxiety scores at each wave.

Cognitive biases and psychopathologies	PT	Wave 1		Wave 2		Wave 3	
		r^2 (%)	P	r^2 (%)	P	r^2 (%)	P
Memory bias	*0.01*	.0150 (1.5%)	**.016***	.0388 (3.88%)	**.0002***	.0134 (1.34%)	**.038***
	0.05	.0166 (1.66%)	**.011***	.0141 (1.41%)	**.027***	.0044 (0.44%)	.233
Positive memory bias	*0.01*	.0159 (1.59%)	**.013***	.0153 (1.53%)	**.021***	.0122 (1.22%)	**.048***
	0.05	.0171(1.71%)	**.010***	.0133 (1.33%)	**.031***	.0032 (0.32%)	.313
Negative memory bias	*0.01*	.0082 (0.82%)	.074	.0290 (2.90%)	**.001***	.0130 (1.30%)	**.041***
	0.05	.0049 (0.49%)	.167	.0088 (0.88%)	.079	.0043 (0.43%)	.242
Social interpretation bias	*0.01*	.0143 (1.43%)	**.019***	.0328 (3.28%)	**.001***	.0209 (2.09%)	**.011***
	0.05	.0113 (1.13%)	**.036***	.0211 (2.11%)	**.007***	.0125 (1.25%)	**.048***
Positive social interpretation bias	*0.01*	.0202 (2.02%)	**.005***	.0180 (1.80%)	**.012***	.0186 (1.86%)	**.016***
	0.05	.0164 (1.64%)	**.012***	.0141 (1.41%)	**.027***	.0067 (0.67%)	.149
Negative social interpretation bias	*0.01*	.0035 (0.35%)	.246	.0223 (2.23%)	**.005***	.0082 (0.82%)	.111
	0.05	.0027 (0.27%)	.312	.0126 (1.26%)	**.036***	.0076 (0.76%)	.125
Non-social interpretation bias	*0.01*	.006 (0.60%)	.129	.0036 (0.36%)	.267	.0025 (0.25%)	.379
	0.05	.0068 (0.68%)	.105	.0031 (0.31%)	.301	.0021 (0.21%)	.419
Positive non-social interpretation bias	*0.01*	.0105 (1.05%)	**.044***	.0001 (0.01%)	.837	.0014 (0.14%)	.506
	0.05	.0072 (0.72%)	.096	.0008 (0.08%)	.607	.0006 (0.06%)	.669
Negative non-social interpretation bias	*0.01*	.0003 (0.03%)	.715	.0055 (0.55%)	**.167***	.0011 (0.11%)	.559
	0.05	.0017 (0.17%)	.423	.0027 (0.27%)	.332	.0016 (0.16%)	.482
Depression symptom scores	*0.01*	.0042 (0.42%)	.202	.0301 (3.01%)	**.001***	.0202 (2.02%)	**.013***
	0.05	.0113 (1.13%)	**.036***	.0256 (2.56%)	**.003***	.0254 (2.54%)	**.005***
Anxiety symptom scores	*0.01*	.0225 (2.25%)	**.003***	.0496 (4.96%)	**$2.71x10^{-5}$***	.0323 (3.23%)	**.002***
	0.05	.0227 (2.27%)	**.003***	.0350 (3.50%)	**$4.39x10^{-4}$***	.0326 (3.26%)	**.002***

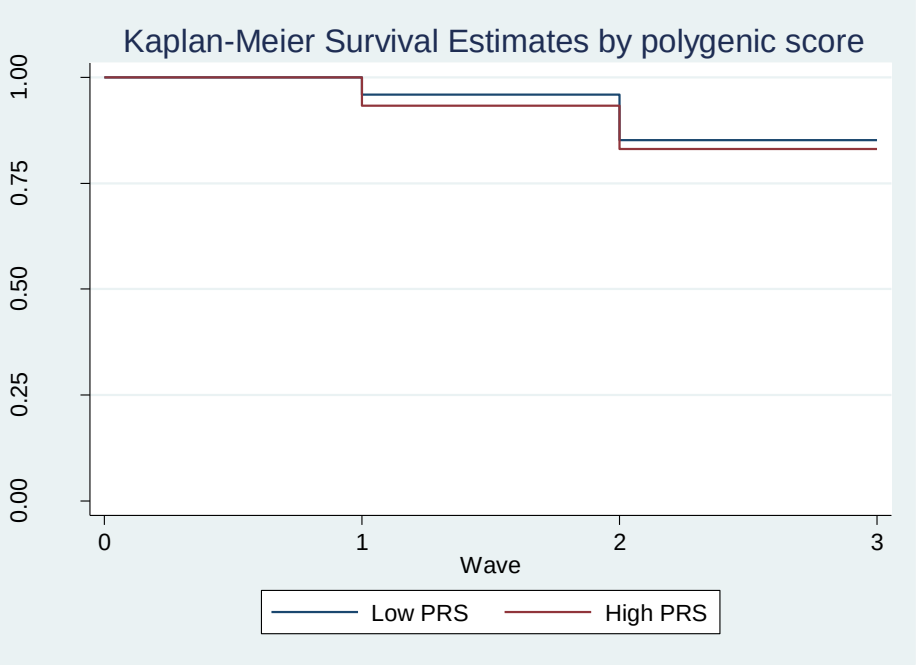
Note: The table above displays the variance explained (r^2) and *p*-values at each of the three waves for all cognitive biases and their positive and negative components. Results are given at the two most significant *p*-value thresholds (PT).

Figure 5.3. Bar charts displaying the variance explained by the MDD PRS at p-value thresholds 0.05, 0.3, 1 for all cognitive biases and their components. Each bar chart shows variance explained for both the full sample, and for only those who provided data at all three time points.



With the exception of the variance explained for positive social interpretation bias by the MDD PRS, all analysis regarding the differences between the full sample and that of those who were present at all three waves of data collection demonstrated relatively small albeit stable effects across the three waves. These findings also suggest that the distinct drop in significance seen in **Figure 5.2** at both wave 2 and 3 is not due to a lack of significant association but rather a lack of power as the numbers of returning participants deceased from wave 1 to wave 2, and further still from wave 2 to wave 3. To examine this further, survival analysis was conducted with a specific focus on those with high and low polygenic scores as defined by high and low median split (**Figure 5.4**).

Figure 5.4. Displaying survival estimates across each of the three waves for those with high and low MDD PRS.



Survival analysis revealed that there was no significant difference between the high and low PRS groups (HR=1.23, 95%CI=.95-1.59, *p*=.113). However, the current sample was limited by its relatively small initial sample size and it is likely that any drop in the retention rate between waves, particularly in terms of those with a higher PRS, had a significant effect on the associations at wave two and three.

5.3.4. Mediation analysis

With main effects having been established between the MDD PRS and cognitive biases (*memory bias* and *social interpretation bias*), and specifically their positive components (*positive memory bias* and *positive social interpretation bias*) as well as depression and anxiety, simple mediation analysis was conducted with depression and anxiety scores as outcomes. These analyses were conducted at the *p*-value thresholds of the MDD PRS (0.01 and 0.05) that explained the highest amount of variance in the cognitive biases and depression and anxiety scores within the CogBIAS sample. These specific thresholds were importantly in keeping with associations found between wave 1 cognitive biases and wave 2 psychopathology, wave 2 cognitive biases and wave 3 psychopathology, and wave 1 cognitive biases and wave 3 psychopathology.

5.3.4.1. Wave 1 cognitive biases on Wave 2 psychopathology.

Mediation models were constructed for those cognitive biases that were found to be significantly associated at wave 1 with both the MDD PRS and depression and anxiety symptoms within the CogBIAS-L-S sample at wave 2. These biases included memory bias, social interpretation bias, and their positive components (i.e., positive memory bias and positive social interpretation bias). The first set of models examined the relationship between the MDD PRS, and wave 2 psychopathology as mediated by each of these biases and their corresponding positive components at wave 1. A total of 346 individuals from the reduced (European only) CogBIAS-L-S sample were included in these analyses (**Tables 5.2**).

Table 5.2. Results from mediation analysis exploring the relationship between the MDD PRS and depression and anxiety scores at wave 2 as mediated by cognitive bias at wave 1.

Wave 1 Bias	Wave 2 Outcome	PT	Pathways			Indirect Effect			Direct Effect			Prop. mediated
			a'	b'	c'	β	std err.	P	β	std err.	P	
Memory bias	Depression	*0.01*	**.15***	**.46***	**.18*(.11)***	.07	.03	**.005***	.10	.05	**.031***	.401
		0.05	**.12***	**.46***	**.16*(.11)***	.06	.03	**.021***	.11	.05	**.030***	.352
	Anxiety	*0.01*	**.15***	**.43***	**.23*(.16)***	.07	.02	**.006***	.16	.05	**.001***	.287
		0.05	**.12***	**.44***	**.20*(.14)***	.05	.02	**.023***	.14	.05	**.004***	.274
Positive memory bias	Depression	*0.01*	**-.12***	**-.30***	**.18*(.14)***	.04	.02	**.028***	.13	.05	**.008***	.211
		0.05	**-.11***	**-.30***	**.16*(.12)***	.03	.02	.056	.13	.05	**.012***	.197
	Anxiety	*0.01*	**-.12***	**-.26***	**.23*(.20)***	.03	.02	**.033***	.20	.05	**$1.9x10^{-4}$***	.139
		0.05	**-.11***	**-.27***	**.19*(.16)***	.03	.02	.061	.17	.05	**.002***	.146
Social int. bias	Depression	*0.01*	**.14***	**.36***	**.18*(.13)***	.05	.02	**.015***	.13	.05	**.009***	.279
		0.05	**.11***	**.37***	**.16*(.12)***	.04	.02	.052	.13	.05	**.014***	.242
	Anxiety	*0.01*	**.14***	**.35***	**.23*(.18)***	.05	.02	**.015***	.19	.05	**$3.8x10^{-4}$***	0.21
		0.05	**.11***	**.36***	**.19*(.16)***	.04	.02	.053	.16	.05	**.003***	.202
Positive social int. bias	Depression	*0.01*	**-.17***	**-.21***	**.18*(.15)***	.04	.02	**.012***	.15	.05	**.007***	.203
		0.05	**-.15***	**-.22***	**.16*(.13)***	.03	.01	**.021***	.13	.05	**.013***	.199
	Anxiety	*0.01*	**-.17***	**-.16***	**.23*(.21)***	.03	.01	**.032***	.21	.06	**$1.7x10^{-4}$***	.115
		0.05	**-.15***	**-.17***	**.19*(.17)***	.03	.01	**.040***	.17	.06	**.002***	.128

Note: The table above shows the a' b' and c' pathway as well as the beta coefficients, standard error (std err.), and p-values (P) for both the indirect and direct effects of the mediation at two p-value thresholds (PT). The proportion mediated (Prop. mediated) through the biases on both depression and anxiety scores within the CogBIAS sample are also given.

The table above highlights that for depression, the most significant indirect effect between the MDD PRS and depression score at wave 2 was through memory bias at threshold 0.01, of which 40.1% was mediated. Wave 1 memory bias at the same threshold was also found to be the most significant mediator of the association between the MDD PRS and anxiety score at wave 2. Following these analyses, both these findings were assessed in more depth in order to examine the validity of these mediations, including any potential reverse causality or reciprocal relationships. This was achieved by assessing the most significant mediations models, and also examining the reverse effects of the psychopathology at wave 1 as a potential mediator of the cognitive bias at wave 2. These models are illustrated below in **Figure 5.5** and **Figure 5.6**.

Figure 5.5. Mediation models showing, **(a)** the effect of memory bias at wave 1 as mediating the effect of the MDD PRS (PT 0.01) on depression at wave 2 and, **(b)** the reverse effect of depression at wave 1 mediating the association between the MDD PRS (PT 0.01) and memory bias at wave 2.

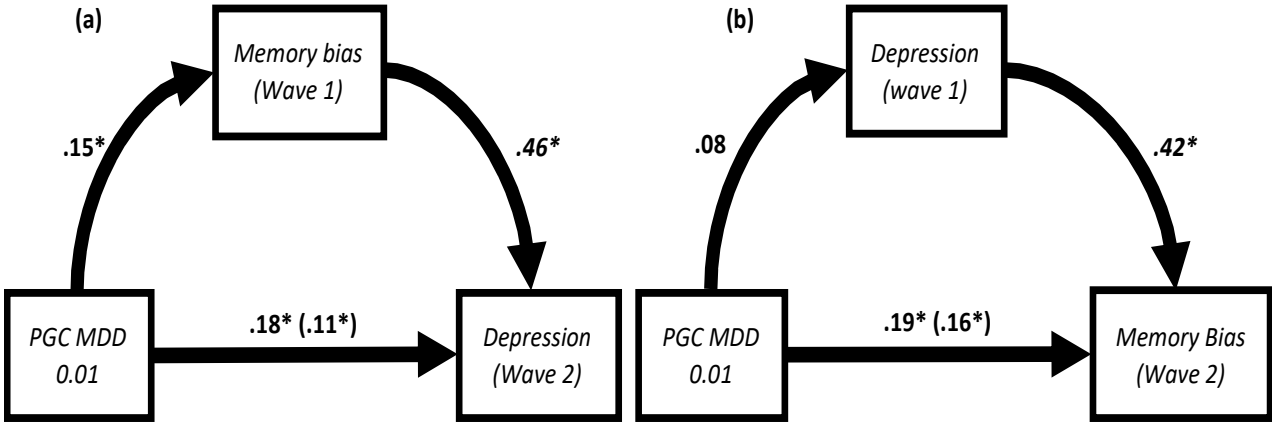
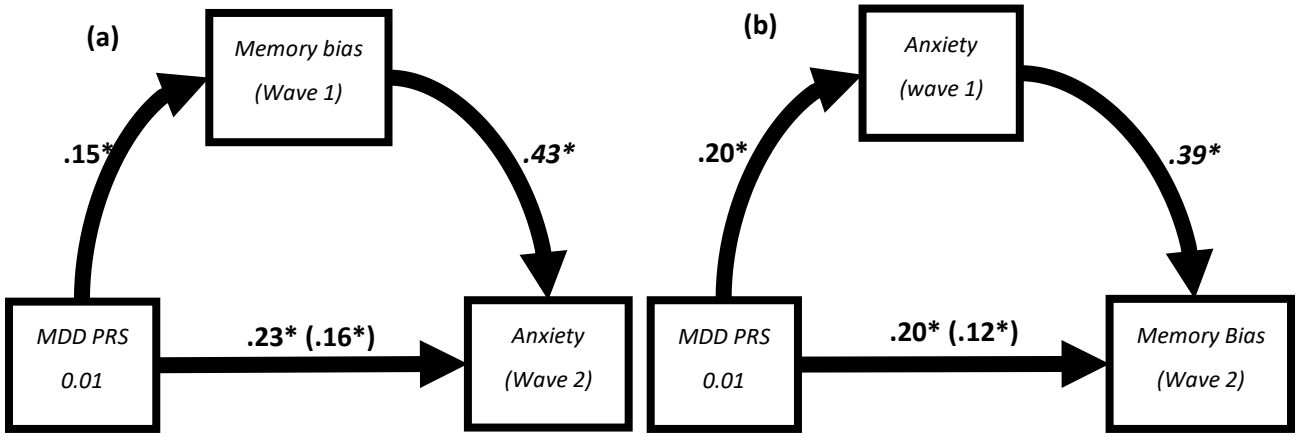


Figure 5.6. Mediation models showing, **(a)** the effect of wave 1 memory bias as mediating the effect of the MDD PRS (PT 0.01) on depression at wave 2 and, **(b)** the reverse effect of depression at wave 1 mediating the association between the MDD PRS (PT 0.01) and memory bias at wave 2.



In **Figure 5.5(a)** the significant mediating effects of memory bias at wave one on depression score at wave two highlight a significant positive association between both the MDD PRS (PT 0.01) and memory biases at wave one (β=.15, 95%CI=.05-.26, *p*=.004), as well as a significant positive direct effect on depression scores at wave two (β=.18, 95%CI=.06-.28, *p*=.001). These results indicate that, in both cases, the MDD PRS (PT 0.01) is associated with an

increased negative bias in memory at wave one and an increased depression score at wave two. The pathway between memory bias at wave one and depression at wave two was also significant with a positive direction of effect (β=.46, 95%CI=.36-.56, p=2.26x10^{-18}), thereby indicating that a negative memory bias at wave one increased depression scores at wave two. However, despite a drop in the coefficient, the direct effect between the MDD PRS and depression scores at wave 2 remained significant when accounting for this mediating effect of memory bias at wave one (β=.11, 95%CI=.01-.20, p=.032). Therefore, the MDD PRS continued to significantly increase depression scores at wave two despite the mediating effects of memory bias at wave one.

In **Figure 5.5(b)**, examining the inverse relationship between the same mediator and outcome, the pathway between the MDD PRS (PT 0.01) and depression score at wave one was non-significant (β=.08, 95%CI=-.03-.18, p=.133). However, the MDD PRS (PT 0.01) did have a significant direct effect on memory bias at wave two (β=.20, 95%CI=.09-.30, p=2.20x10^{-4}). Furthermore, although depression score at wave one did not mediate the relationship between genetic risk for depression and memory bias at wave two, there was a significant association between depression score at wave one and memory bias at wave two (β=.42, 95%CI=.32-.51, p=7.28x10^{-17}). The direct effect also remained significant when controlling for mediating effects of depression at wave one (β=.16, 95%CI=.07-.26, p=.001). However, the lack of a significant association between the MDD PRS and depression at wave one may suggests a reciprocal relationship between memory bias and depression. The proportion of the total effect that was mediated by depression was 17.4%, which was considerably less than the 40.1% observed in the original model illustrated in **Figure 5.5(a)**.

The significant effects of memory bias at wave one as mediating the relationship between the MDD PRS (PT 0.01) on anxiety score at wave two was also explored in **Figure 5.6(a)**. In this model, the association between the MDD PRS (PT 0.01) and memory biases at wave one was significant and had a positive direction of effect (β=.15, 95%CI=.05-.26, p=.004), increasing a negative bias in memory at wave one. This was also the case for the direct effect between genetic risk for depression and anxiety scores at wave two (β=.23, 95%CI=.12-.34, p=2.71x10^{-5}), with the MDD PRS (PT 0.01) associated with increased anxiety scores at wave two. The relationship between memory bias at wave one and anxiety scores at wave two also showed a significant positive association (β=.43, 95%CI=.33-.53, p=1.36x10^{-15}), with memory bias at wave one

significantly increasing anxiety scores at wave two. The direct effect between depression risk and anxiety at wave two also remained significant with the same direction of effect (β=.16, 95%CI=.06-.26, *p*=.001).

Examining the inverse of this relationship illustrated in **Figure 5.6(b)**, the pathway between the MDD PRS (PT 0.01) and anxiety scores at wave one was found to have a significant positive association (β=.20, 95%CI=.09-.30, $p=3.19x10^{-4}$), with the MDD PRS (PT 0.01) driving increases in anxiety scores. This was also the case regarding the direct effect on memory bias at wave two (β=.20, 95%CI=.09-.30, $p=2.20x10^{-4}$), with the MDD PRS (PT 0.01) increasing a negative memory bias at wave two to an almost identical extent. The relationship between anxiety scores at wave one and memory bias at wave two also displayed a significant positive association (β=.39, 95%CI=.30-.49, $p=1.30x10^{-14}$), with anxiety scores associated with increases in negative memory bias. Once again, the direct association between the MDD PRS (PT 0.01) and memory bias at wave two remained significant with a positive direction of effect (β=.12, 95%CI=.02-.22, *p*=.016), suggesting that the MDD PRS (PT 0.01) continued to significantly increase a negative bias in memory at wave two despite the mediating effects of anxiety score at wave one. The proportion of the total effect that was mediated by anxiety in the inverse model was 39.2%, which was more than the 28.7% from the original model in **Figure 5.6(a)**.

5.3.4.2. Wave 2 cognitive biases on Wave 3 psychopathology

Following on from the assessment of cognitive biases at wave one as mediating the effects of genetic risk for depression on psychopathology at wave two, the current study proceeded to examine associations between waves two and three. Specifically, it was examined whether significant associations between the MDD PRS and cognitive biases at time point two mediated the same relationship between the MDD PRS and psychopathologies depression and anxiety at wave three. A total of 289 individuals from the reduced (European only) CogBIAS-L-S sample were included in these analyses. The results of these analyses are given below in **Table 5.3**.

Table 5.3. Results from mediation analysis exploring the relationship between the MDD PRS and depression and anxiety scores at wave 3 as mediated by cognitive bias at wave 2.

Wave 2 Bias	Wave 3 Outcome	PT	Pathways			Indirect Effect			Direct Effect			Prop. mediated
			a'	b'	c'	β	std err.	P	β	std err.	P	
Memory bias	Depression	*0.01*	**.14***	**.53***	**.14***(.06)	.08	.03	**.016***	.06	.05	.207	.540
		0.05	**.07**	**.54***	**.15*(12)***	.04	.03	.272	.12	.05	**.022***	.229
	Anxiety	*0.01*	**.14***	**.39***	**.19*(.14)***	.05	.02	**.020***	.14	.05	**.011***	.286
		0.05	.07	**.40***	**.20*(.18)***	.03	.02	.275	.18	.06	**.001***	.129
Positive memory bias	Depression	*0.01*	**-.13***	**-.25***	**.14***(.11)	.03	.02	**.045***	.11	.06	.065	.238
		0.05	-.11	**-.25***	**.15*(13)***	.03	.02	.103	.13	.06	**.031***	.175
	Anxiety	*0.01*	**-.13***	**-.18***	**.19*(.17)***	.02	.01	.070	.17	.06	**.003***	.120
		0.05	-.11	**-.18***	**.20*(.19)***	.19	.06	**.002***	.20	.06	**.001***	.093
Negative memory bias	Depression	*0.01*	.11	**.53***	**.14***(.08)	.06	.03	.070	.08	.05	.103	.418
		0.05	.04	**.53***	**.15*(.13)***	.02	.03	.511	.13	.05	**.009***	.142
	Anxiety	*0.01*	.11	**.40***	**.19*(.15)***	.04	.02	.074	.15	.05	**.005***	.227
		0.05	.04	**.41***	**.20*(.19)***	.02	.03	.512	.19	.05	**.001**	.082
Social int. bias	Depression	*0.01*	**.16***	**.44***	**.13***(.06)	.07	.03	**.007***	.06	.05	.252	.540
		0.05	.11	**.44***	**.15***(.11)	.05	.03	.073	.11	.06	.058	.316
	Anxiety	*0.01*	**.16***	**.43***	**.18*(.11)***	.07	.03	**.007***	.11	.05	**.033***	.377
		0.05	.11	**.43***	**.19*(.15)***	.05	.03	.074	.15	.05	**.006***	.236
Positive social int. bias	Depression	*0.01*	-.10	**-.15***	**.13*(.12)***	.02	.01	.152	.12	.06	**.042***	.114
		0.05	-.08	**-.16***	**.15*(.14)***	.01	.01	.219	.14	.06	.020	.083
	Anxiety	*0.01*	-.10	**-.17***	**.18*(.17)***	.02	.01	.139	.17	.06	**.004***	.091
		0.05	-.08	**-.17***	**.20*(.18)***	.01	.01	.209	.18	.06	**.002**	.077
Negative social int. bias	Depression	*0.01*	**.15***	**.49***	**.13***(.06)	.07	.03	**.012***	.06	.05	.240	.539
		0.05	.09	**.49***	**.15*(.11)***	.04	.03	.142	.11	.05	**.040***	.280
	Anxiety	*0.01*	**.15***	**.45***	**.18*(.12)***	.07	.03	**.013***	.12	.05	**.027***	.364
		0.05	.09	**.46***	**.20*(.16)***	.04	.03	.143	.16	.05	**.003**	.202

Note: The table above shows the a' b' and c' pathway as well as the regression beta coefficients, standard error (std err), and p-values (P) for both the indirect and direct effects of the mediation at two p-value thresholds (PT). The proportion mediated (Prop. mediated) through the biases are also given.

The table above highlights that social interpretation bias at wave two was the most significant mediator regarding the relationship between the MDD PRS (PT 0.01) and both depression and anxiety scores, with 54% and 37.7% proportion mediated respectively. As before,

both these findings were assessed in more depth in order to examine the validity of these mediations, including any potential reverse causality or reciprocal relationships. These models are illustrated below in **Figure 5.7** and **Figure 5.8**.

Figure 5.7. Mediation models showing, **(a)** the effect of wave 2 social interpretation bias as mediating the effect of the MDD PRS (PT 0.01) on depression at wave 3 and, **(b)** the reverse effect of depression at wave 2 mediating the association between the MDD PRS (PT 0.01) and social interpretation bias at wave 3.

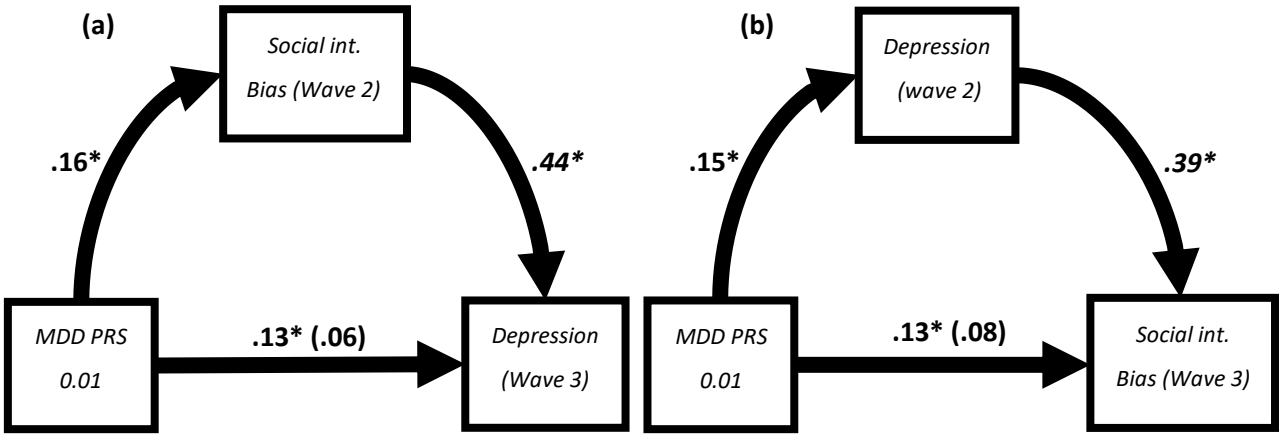
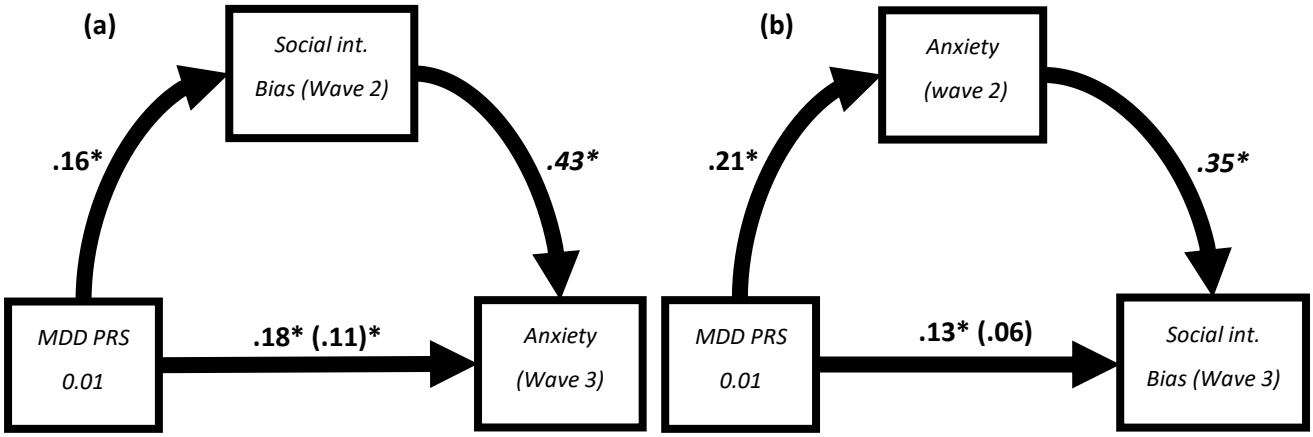


Figure 5.8. Mediation models showing, **(a)** the effect of wave 2 social interpretation bias as mediating the effect of the MDD PRS (PT 0.01) on anxiety at wave 3 and, **(b)** the reverse effect of anxiety at wave 2 mediating the association between the MDD PRS (PT 0.01) and social interpretation bias at wave 3.



In **Figure 5.7(a)** social interpretation bias at wave two is demonstrated as significantly mediating the effects of the MDD PRS (PT 0.01) on depression at wave three. In this model the

MDD PRS (PT 0.01) had a significant positive association with social interpretation bias (β=.16, 95%CI=.05-.28, *p*=.005) increasing a negative bias in social interpretation, whilst also having a significant positive direct effect on depression at wave three (β=.13, 95%CI=.02-.25, *p*=.023), thereby increasing depression score at this wave. The relationship between social interpretation bias at wave two and depression at wave three was also significant with a positive direction of effect (β=.44, 95%CI=.34-.55, $p=1.8x10^{-14}$), suggesting that this bias at wave two is associated with increased depression score at wave three. Furthermore, the previously positive significant direct effect between the MDD PRS (PT 0.01) and depression at wave three was no longer significant when the mediating effects of social interpretation bias were accounted for (β=.06, 95%CI=-.04-.17, *p*=.254).

When examining the inverse of this mediating relationship, illustrated in **Figure 5.7(b)**, a similar pattern of finding emerged. The pathway between the MDD PRS (PT 0.01) and depression score at wave two was found to have a significant positive association (β=.15, 95%CI=.03-.26, *p*=.008). This was also true for the direct effect of the MDD PRS (PT 0.01) on social interpretation bias at wave three (β=.13, 95%CI=.02-.24, *p*=.018). These results indicate that the MDD PRS significantly increases both depression score at wave two and a negative social interpretation bias at wave three. The association between depression scores at wave two and social interpretation bias at wave three was also found to have a significant positive association (β=.39, 95%CI=.28-.50, $p=4.39x10^{-12}$), with depression increasing a negative bias in social interpretation to a slightly lesser extent than the same pathway in **Figure 5.7(a)**. However, the direct effect between the MDD PRS (PT 0.01) and social interpretation bias at wave three was found to be non-significant when the mediating effects of depression at wave two were accounted for (β=.08, 95%CI=-.03-.18, *p*=.150). Here, the proportion of the total effect mediated by depression in the inverse model was 43.4%, which was slightly less than the 54% from the original model in **Figure 5.7(a)**.

In **Figure 5.8(a)** the MDD PRS (PT 0.01) was shown to have a significant positive effect on social interpretation bias at wave two (β=.16, 95%CI=.05-.28, *p*=.005), thereby increasing a negative bias in social interpretation at this wave. This was also the case regarding the direct relationship between the MDD PRS (PT 0.01) and anxiety scores at wave three (β=.18, 95%CI=.07-.30, *p*=.002), with the MDD PRS (PT 0.01) significantly associated with an increase in anxiety scores at this wave. The effect of a negative social interpretation bias at wave two had

a significant and positive association with anxiety scores at wave three (β=.43, 95%CI=.32-.53, p=1.54x10^{-13}), increasing anxiety scores at wave three as a result. However, despite a drop in the association regarding the direct effect there still remained a significant direct association between MDD PRS (PT 0.01) on anxiety score at wave three (β=.11, 95%CI=.01-.22, p=.034) when accounting for the mediating effects of social interpretation bias.

The inverse of this relationship as illustrated in **Figure 5.8(b)**, highlights a significant positive association between the MDD PRS (PT 0.01) and anxiety scores at wave two (β=.21, 95%CI=.10-.32, p=1.76x10^{-4}), with the MDD PRS (PT 0.01) increasing anxiety scores at this wave. The direct effect between the MDD RS (PT 0.01) and social interpretation bias at wave three was also significant with a positive direction of effect (β=.13, 95%CI=.02-.24, p=.018), increasing a negative bias in social interpretation at this wave. Anxiety scores at wave two were also shown to have a significant and positive effect on social interpretation bias at wave three (β=.35, 95%CI=.24-.46, p=1.34x10^{-9}), significantly increasing a negative social interpretation bias. In this case however, the mediating effects of anxiety scores at wave two rendered the direct effect between the MDD PRS (pt 0.01) and social interpretation bias at wave three non-significant (β=.06, 95%CI=-.05-.17, p=.266). The proportion of the total effect mediated by anxiety in the inverse model was 54.9%, which was considerably more than the 37.7% from the original model in **Figure 5.8(a)**.

5.3.4.3. Wave 1 cognitive biases on Wave 3 psychopathology

Having assessed the mediating effects of the cognitive biases and their components, between timepoints one and two, and two and three, further simple mediation analysis was conducted from timepoint one to timepoint three. For this analysis mediation models were used to examine the effects of those biases significantly associated with the MDD PRS at timepoint one as mediating the genetic risk for depression and depression and anxiety score at timepoint three. The total number of individuals included in these analyses ranged from 303 to 320 depending on the missingness of their phenotypic data. The results of are displayed below in **Table 5.4**.

Table 5.4. Results from mediation analysis exploring the relationship between the MDD PRS and depression and anxiety scores at wave 3 as mediated by cognitive bias at wave 1.

Wave 1 bias	Wave 3 Outcome	PT	Pathways			Indirect Effect			Direct Effect			Prop. mediated
			a'	b'	c'	β	std err.	P	β	std err.	P	
Memory bias	Depression	*0.01*	**.14***	**.40***	**.14***(.09)	.06	.02	**.013***	.09	.05	.101	.396
		0.05	.10	**.40***	**.16*(.13)***	.04	.02	.090	.12	.05	**.020***	.238
	Anxiety	*0.01*	**.14***	**.32***	**.18*(.13)***	.05	.02	**.017***	.13	.05	**.015***	.259
		0.05	.10	**.33***	**.19*(.15)***	.03	.02	.095	.15	.06	**.006***	.174
Positive memory bias	Depression	*0.01*	**-.13***	**-.27***	**.14***(.11)	.03	.02	**.034***	.11	.06	.054	.245
		0.05	-.10	**-.27***	**.16*(.14)***	.03	.02	.090	.14	.06	**.016***	.168
	Anxiety	*0.01*	**-.13***	**-.19***	**.18*(.15)***	.02	.01	.055	.15	.06	**.006***	.137
		0.05	-.10	**-.19***	**.19*(.17)***	.02	.01	.110	.17	.06	**.004***	.107
Social int. bias	Depression	*0.01*	**.14***	**.29***	**.14***(.10)	.04	.02	**.027***	.10	.06	.051	.275
		0.05	.08	**.29***	**.17*(.14)***	.02	.02	.168	.14	.06	**.012***	.145
	Anxiety	*0.01*	**.14***	**.24***	**.17*(.14)***	.03	.02	**.034***	.14	.06	**.010***	.186
		0.05	.08	**.24***	**.18*(.16)***	.02	.01	.174	.16	.06	**.004***	.112
Positive social int. bias	Depression	*0.01*	**-.18***	**-.14***	**.14*(.12)***	.03	.01	**.049***	.12	.06	**.041***	.182
		0.05	**-.13***	**-.15***	**.17*(.15)***	.02	.01	.091	.15	.06	**.012***	.116
	Anxiety	*0.01*	**-.18***	-.05	**.17*(.16)***	.01	.01	.371	.16	.06	**.004***	.055
		0.05	**-.13***	-.06	**.18*(.17)***	.01	.01	.327	.17	.06	**.003***	.045

Note: The table above shows the a' b' and c' pathway as well as the regression beta coefficients, standard error (std err.), and p-values for both the indirect and direct effects of the mediation at two p-value thresholds (PT). The proportion mediated (Prop. mediated) through the biases are also given.

The findings in **Table 5.4** highlight memory bias at wave one as being the most significant mediator of the relationship between the MDD PRS (PT 0.01) and both depression and anxiety score at wave three, with 39.6% and 25.9% of proportion mediated respectfully. These models were assessed in more depth as before, and are illustrated in **Figure 5.9** and **Figure 5.10**.

Figure 5.9. Mediation models showing, **(a)** the effect of wave 1 memory bias as mediating the effect of the MDD PRS (PT 0.01) on depression at wave 3 and, **(b)** the reverse effect of depression at wave 1 mediating the association between the MDD PRS (PT 0.01) and memory bias at wave 3.

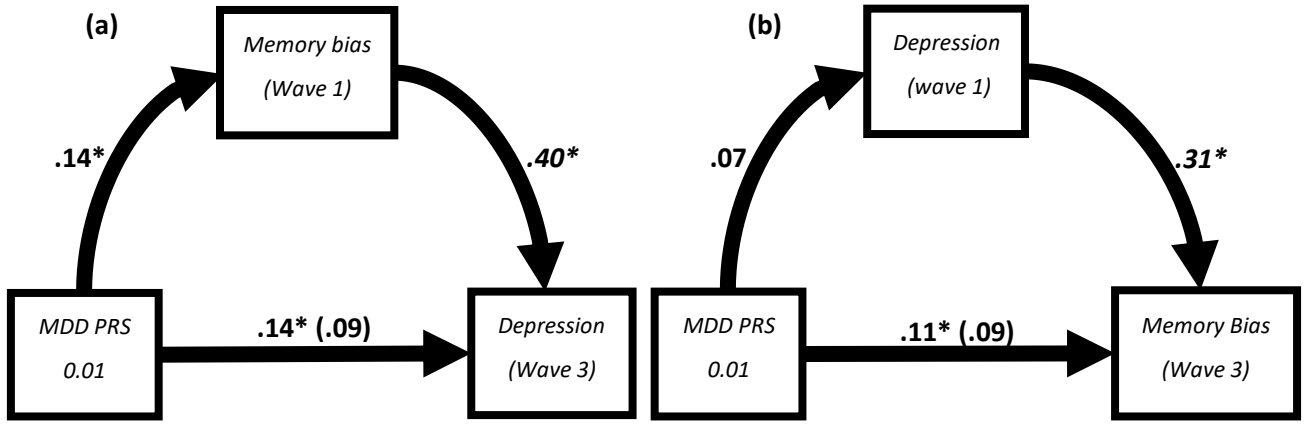
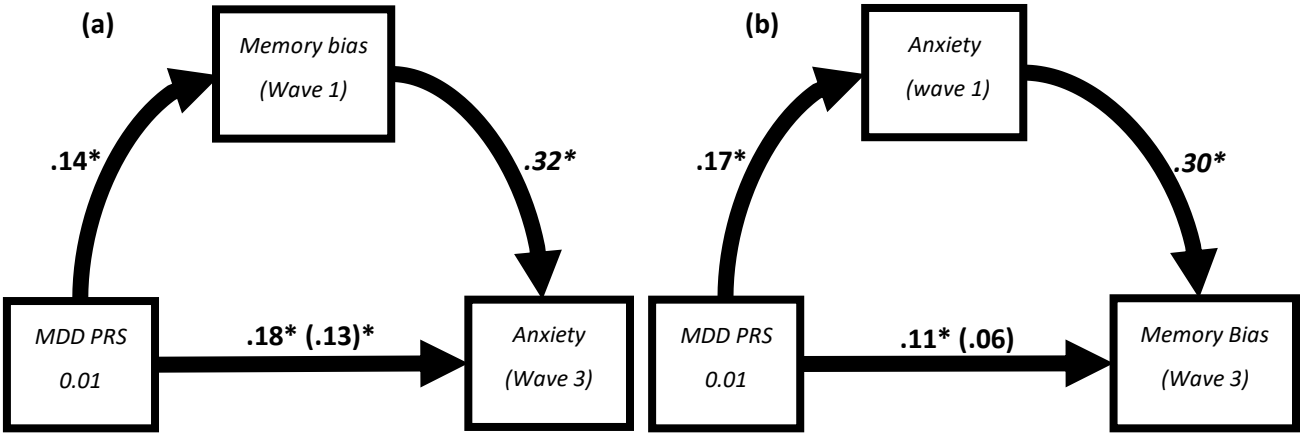


Figure 5.10. Mediation models showing, **(a)** the effect of wave 1 memory bias as mediating the effect of the MDD PRS (PT 0.01) on anxiety at wave 3 and, **(b)** the reverse effect of anxiety at wave 1 mediating the association between the MDD PRS (PT 0.01) and memory bias at wave 3.



In **Figure 5.9(a)** the MDD PRS (PT 0.01) is shown as having a significant positive association with memory bias at wave one (β=.14, 95%CI=.04-.25, *p*=.009), increasing a negative bias in memory at this wave. The direct effect of the MDD PRS (PT 0.01) was also shown to have a significant positive effect on depression scores at wave three (β=.14, 95%CI=.03-.26, *p*=.011), increasing depression scores at this wave. Memory bias at wave one also had a significant positive association with depression at wave three (β=.40, 95%CI=.29-.50, $p=5.62x10^{-12}$), resulting in an increase in depression scores at wave three. Furthermore, the previously significant direct effect

between the MDD PRS (PT 0.01) and depression at wave three dropped out of significance when these mediating effects were taken into account (β=.09, 95%CI=-.02-.19, *p*=.102).

When assessing the inverse of this mediating relationship shown in **Figure 5.9(b)** the pathway regarding the association between the MDD PRS (PT 0.01) and depression scores at wave one had a non-significant positive effect (β=.07, 95%CI=-.04-.18, *p*=.212). However, there was a significant positive direct effect between the MDD PRS (PT 0.01) and memory bias at wave three (β=.11, 95%CI=.01-.22, *p*=.034), increasing a negative memory bias at this wave. Depression at wave one was also found to have a significant positive effect on memory bias at wave three (β=.31, 95%CI=.21-.41, $p=6.87x10^{-9}$), with the effect shown as increasing a negative memory bias at wave three. Similar to **Figure 5.9(a)**, the direct effect of the MDD PRS (PT 0.01) on memory bias at wave three dropped out of significant when accounting for these mediating effects (β=.09, 95%CI=-.01-.19, *p*=.070). The proportion of the total effect mediated by depression in the inverse model was 18.6%, which was considerably less than the 39.6% from the original model in **Figure 5.9(a)**.

In **Figure 5.10**, exactly the same dependant variable and mediator were assessed for their effects on anxiety at wave three. In **Figure 5.10(a)** the MDD PRS (PT 0.01) is shown as having a significant positive effect on memory bias at wave one (β=.14, 95%CI=.04-.25, p=.009), increasing a negative bias in memory. The direct effect of the MDD PRS also had a significant positive effect on anxiety scores at wave three (β=.18, 95%CI=.07-.29, *p*=.002), increasing anxiety scores at this wave. The association between memory bias at wave one on anxiety scores at wave three was again found to have a significant positive effect (β=.32, 95%CI=.21-.43, $p=2.83x10^{-8}$), with wave one memory bias increasing anxiety scores at wave three. However, in this instance the direct effect of the MDD PRS (PT 0.01) on wave three anxiety remained significant when accounting for the mediation (β=.13, 95%CI=.03-.24, *p*=.015).

When examining the inverse of this relationship shown in **Figure 5.10(b)** the pathway between the MDD PRS (PT 0.01) and anxiety score at wave one was found to be significant with a positive direction of effect (β=.17, 95%CI=.06-.27, *p*=.002), as was the direct effect on memory bias at wave three (β=.11, 95%CI=.01-.22, *p*=.034). In both cases the effect of the MDD PRS (PT 0.01) increased anxiety scores at wave one and a negative memory bias at wave three. The association between anxiety scores at wave one and memory bias at wave three also had a

significant positive effect (β=.30, 95%CI=.19-.40, p=4.08x10^{-8}), with anxiety scores at wave one increasing a negative memory bias at wave three. However, the direct effect between MDD PRS (PT 0.01) and memory bias was non-significant after controlling for these mediating effects (β=.06, 95%CI=-.03-.16, p=.219). The proportion of the total effect mediated by anxiety in the inverse model was 44%, which was considerably more than the 25.9% from the original model in **Figure 5.10(a)**.

5.4. Discussion

Continuing with the comprehensive test of the CogBIAS hypothesis (Fox & Beevers, 2016), the current chapter aimed to address the hypothesis that cognitive biases exist on a pathway between genetic risk and psychopathology. More specifically, associations between a clinically defined MDD PRS (N. R. Wray et al., 2018), cognitive biases in interpretation and memory, and symptoms of depression and anxiety were examined in the same CogBIAS-L-S sample of 12-16-year-old children that was assessed in the previous chapter. These associations, examined across three time points, were assessed across time, as moderated by time, and at each time point including an assessment of the proportion of variance explained by the MDD PRS. Significant associations were then probed further to assess whether specific cognitive biases and their positive and negative components mediated the association between the MDD PRS and both depression and anxiety. Hypotheses and results related to these aims are discussed in detail below.

5.4.1. Effect of the MDD PRS on cognitive biases and self-reported depression and anxiety scores

It was hypothesized that the MDD PRS would be positively associated with both depression and anxiety, and cognitive biases in memory and interpretation within the CogBIAS-L-S sample. By taking a mixture model approach to the analyses, and combining data from each participant across the three waves, the current study was able to increase the effective sample size, and with it the power to detect effects of the MDD PRS within the CogBIAS sample. In keeping with the hypothesis, the MDD PRS was found to have nominally significant associations, across multiple thresholds, with depression scores within the sample, with one threshold (pt 0.05) remaining significant following multiple testing corrections, whilst another (pt 0.01) failed to reach nominal significance. Cross-sectional analysis also revealed several nominally significant associations between the MDD PRS and depression scores at each wave as well as two thresholds (pt 0.01 and pt 0.05) at wave two that survived multiple testing correction. The variance explained reached up to 3.01% at wave two, at a p-value threshold of 0.01. Unexpectedly, although in line with the hypothesis, the MDD PRS was also significantly more associated with anxiety scores within the sample, remaining significant following multiple testing correction at all thresholds. Furthermore, wave two also saw the MDD PRS explain variance in anxiety scores of up to 4.96% at a *p*-value threshold of 0.01. This is the first time an adult MDD PRS has been used to predict variation in depression or anxiety scores within a sample of children. It is also significant to note

that the proportion of variance explained in the current study are comparable to those of previous studies of adults both within and across disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Demirkan et al., 2011).

The finding that the MDD PRS significantly predicts both self-reported anxiety and depression is in keeping with previous twin studies (Eley & Stevenson, 1999; J. L. Silberg, Rutter, & Eaves, 2001; Thapar & McGuffin, 1997) and molecular genetic research (Demirkan et al., 2011; Okbay et al., 2016) that has found strong genetic correlations between these two psychopathologies in both children and adolescents. Furthermore, as the MDD PRS was significantly more associated with anxiety than depression the current findings can also be seen as in keeping with the previously suggested notion that anxiety may act as a precursor to depression onset (Avenevoli, Stolar, Li, Dierker, & Merikangas, 2001; Maria Kovacs, Gatsonis, Paulauskas, & Richards, 1989; Orvaschel, Lewinsohn, & Seeley, 1995; Woodward & Fergusson, 2001). Evidence supporting this has also been reported in a study assessing the trajectory of phenotypes within the CogBIAS-L-S sample used in the current study (Booth et al, 2019). Here, findings highlighted that whilst anxiety symptoms showed no increase across the three waves, there was a significant increase in depression symptoms, suggesting that anxiety onset had already peaked by the first wave. It is therefore likely that despite the shared genetic architectures between the two psychopathologies, the limited association between the MDD PRS and depression scores compared to anxiety scores was simply because symptoms of depression were yet to set in. However, it could also be suggested that evidence for an association between early anxiety and later depression merely reflects the significant genetic overlap between both depression and anxiety. In support of this hypothesis, a longitudinal twin study assessing 676 twins at two timepoints found no evidence for anxiety being aetiologically distinct from depression, and increasing the risk of depressive symptoms in later life (Rice, van den Bree, & Thapar, 2004). Instead, the authors suggested that a covariation across the timepoints was due to the shared genetic and environmental architectures of the two psychopathologies. It may be possible that this shared genetic aetiology may function as an indirect genetic effect through an individual's behavioural traits, including cognitive biases, resulting in gene-environment correlation and interaction which then drives an outcome of either depression or anxiety. However, further longitudinal research, with a significantly larger sample, more timepoints, whole-genome data and valid environmental measures will be required to examine this possibility.

The MDD PRS was also significantly associated with several cognitive biases, which was again in line with the hypothesis of the current study. Furthermore, the initial mixture model suggested that these effects were driven by a negative association between the MDD PRS and the positive components of these biases (*positive memory bias* and *positive social interpretation bias*), resulting in a reduction in positive words endorsed and recalled in the SRET task, and reductions in the interpretation of social events as positive. This is particularly interesting as it has been suggested that depressed individuals, compared to their healthy counterparts lack a positive interpretation bias (Alloy & Abramson, 1979; McKendree-Smith & Scogin, 2000). This suggestion is in line with findings from the mixture model, as a lack of positive interpretation bias specific to social contexts was robustly associated with genetic risk for depression. Cross-sectional analysis at each wave further highlighted that the MDD PRS was associated with an increased negative memory and social interpretation bias, explaining variance of up to 3.88% and 3.28% respectively, both at p-value threshold 0.01 at wave 2. However, at this particular timepoint and threshold, these associations were shown as being driven by the negative components of these biases with variance explained by the MDD PRS reaching 2.90% for the negative component of memory bias (*negative memory bias*), and 2.23% for the negative component of social interpretation bias (*negative social interpretation bias*), compared to 1.53% and 1.80% for their positive counterparts respectively. Despite this spike in association regarding the negative components of memory and social interpretation bias the effects of the positive components were more consistent across the three waves, driving associations at wave one and three for social interpretation bias, with memory bias appearing to be more balanced regarding the influence of both the positive and negative components. Furthermore, unlike the mixture models, cross-sectional analysis is not robust to the effects of dropouts, which was evident across the three waves, and may have influenced the results.

This is the first study of its kind to demonstrate that both a lack of a positive bias, and the presence of a negative bias is associated with an adult genetic risk score for depression, in a sample of adolescents. These finding suggest that cognitive bias modification (CBM) that seeks to reduce symptoms of depression and anxiety by training individuals away from attending to, remembering, or interpreting stimuli as negative should also consider training them towards more positive stimuli as this may have an equal or greater effect. In support of this suggestion, a recent study has demonstrated that a positive memory bias can have a significant protective effect against

symptoms of depression one year on by reducing the negative effect of stressors across time (Askelund, Schweizer, Goodyer, & van Harmelen, 2019a).

The mixture model concerning the MDD PRS-by-time interactions revealed only one nominally significant finding with depression scores at a single threshold (PT 0.01) that did not survive correction for multiple testing. Simple slope analysis demonstrated a partial non-linear interaction with time, with the effect of the MDD PRS significant only at wave two, with the association at wave three falling short of significance, possibly due to a lack of power. The suggestion that a lack of power might have played a role was reinforced by assessing the variance explained cross-sectionally by the MDD PRS in only those present at every wave. The 'completers only' analysis, despite a general drop in variance explained, did highlight increases in variance explained in depression scores across each wave by the MDD PRS indicating that the nominally significant interaction observed in the mixture model, which is also robust to the effects of dropouts, was likely a reliable finding.

Whilst these finding provides partial support for previous research highlighting the increasing heritability of depression over time (Bergen, Gardner, & Kendler, 2007; Lau & Eley, 2006), the initial interaction was nominal and the association at wave three, did not reach statistical significance. This is likely due to the limited statistical power, measures at only three timepoints, and a reduction of nearly a fifth of the sample across the three waves, resulting in the current study being underpowered to accurately detect interaction effects. However, with a larger sample size and increased measures starting at earlier timepoints it is thought that this interaction would survive correction for multiple testing and provide a more conclusive result regarding the stability of the genetic effect on depression over time.

Other than the nominal MDD PRS-by-time interaction regarding depression at a single threshold, no other significant MDD PRS-by-time interactions were observed for any of the cognitive biases or their positive and negative components, or for anxiety scores. This suggests that the effect of the MDD PRS on these phenotypes are stable over time. This finding is also in line with the current study's hypothesis, and the results from Chapter four (study two) highlighting cognitive biases as stable phenotypes, with little change in their expression over time.

Further longitudinal research is required to assess the differential effects of positive and negative biases, and whether these are opposite ends of the same spectrum, or completely separate

co-existing cognitive behavioural traits. It is also essential that earlier timepoints are incorporated with a significantly increased sample size in order to examine the genetic effects on these cognitive biases and depression and anxiety as they develop through early childhood.

5.4.2. Cognitive biases as mediator of genetic risk for major depression

The current study also hypothesized that cognitive biases in memory and interpretation would mediate the association between the MDD PRS and depression and anxiety scores at later waves within the CogBIAS-L-S sample. To that end, and in support of this hypothesis, cognitive biases in memory and social interpretation were found to partially mediate the relationship between the MDD PRS and depression scores at later waves, but not for anxiety scores.

These findings, demonstrating the significant partial mediating effects of both biases, and their positive and negative components on later depression scores were robust and reliable findings as their mediating effects were consistently shown across each and all waves. Furthermore, the findings regarding memory bias at wave one mediating the effect of the MDD PRS on depression scores at both wave two and wave three were also robust to the effects of reverse causality. This was evident as the MDD PRS was not significantly associated with depression when the inverse of these mediation models was examined. This likely suggests that a negative memory bias emerged prior to depression symptoms within the CogBIAS-L-S sample and may lie on a casual pathway between genetic risk for, and an outcome of depression.

There was also evidence for reciprocal relationships between memory and social interpretation bias and depression. However, with the exception of social interpretation bias, there was little evidence for reciprocal mediation effects. That is, memory bias mediated the effects of the MDD PRS on later depression, but depression did not mediate the effects of the MDD PRS on later memory bias. This finding may suggest that MDD genetic risk may initially present as a cognitive bias in memory that, once established, lead to depressive symptoms which further exacerbate the memory bias. This supports the previous suggestion that a memory bias emerges prior to symptoms of depression, and the notion that cognitive biases, and particularly memory bias, may represent a potential causal mechanism and intermediate phenotype for depression. However, due to the reciprocal mediation effects observed, the same cannot be said for social interpretation bias. Disentangling this effect and determining the chronicity of either variable in

terms of which developed first would require earlier measurements of both social interpretation bias and depression scores to assess the emergence of each, and their corresponding effect on one another.

The lack of any significant mediation by cognitive biases on anxiety, that was not the result of reverse causality, is thought to be due to the phenotype already being imbedded within the sample from wave one. This rendered any assessment of anxiety and its developmental trajectory through cognitive biases somewhat redundant due to a lack of measures at earlier timepoints, before anxiety had set in, but at a time when these cognitive biases had formed or were in development. As it has been suggested that anxiety may develop prior to depression (Avenevoli et al., 2001; Maria Kovacs et al., 1989; Orvaschel et al., 1995; Woodward & Fergusson, 2001), measurements at earlier timepoints, before anxiety symptoms present, will likely allow for the assessment of cognitive biases as potential mediators of genetic risk and later anxiety symptoms.

This is the first study to demonstrate, using genome-wide data, that the relationship between adult genetic risk for major depression and adolescent depression symptoms scores are mediated by cognitive biases in memory and interpretation using a longitudinal study design. As such there is little previous research to compare the current findings. However, previous research has shown reciprocal effects between the cognitive bias attribution style and depression, demonstrating consistent longitudinal effects across two timepoints (Lau & Eley, 2008). This could be said to be in keeping with the reciprocal mediating effects of social interpretation bias at wave two in the current study. However, the study by Lau and Eley (2008) used a twin design, and therefore did not include any genome-wide data. More recent research, using a genome-wide approach, has demonstrated longitudinal mediation of the relationship between an MDD PRS and both clinical and self-reported depression (Navrady et al., 2018). However, in this study the relationship was mediated by neuroticism, and with an opposing effect resiliency, which constitute somewhat different phenotypes to the cognitive biases used in the current study.

Replication of findings regarding the relationship between genetic risk for depression and later depression scores as mediated by memory and interpretation bias are required in a larger longitudinal sample with increased power. Future research should also consider more measurements at earlier timepoints in order to disentangle these effects further and capture the developmental trajectory of anxiety to assess whether genetic risk associated with anxiety is

mediated by cognitive biases. Furthermore, replication efforts with an increased sample size should also examine the moderating effects of both positive and negative life events, as these environmental factors likely impact on these mediated associations.

5.4.3. Limitations

Despite the overall success of the current study, confirming the majority of the hypotheses, and providing testament to the strength of the somewhat novel approach used, there are several limitations that should be noted. Firstly, and as highlighted in the previous chapter, the dot-probe task that was used to measure attention bias in the CogBIAS-L-S sample was found to be unreliable (see Chapter 4), meaning that attention bias, yet again, could not be included in these analyses. With the use of a more reliable measure of attention bias, such as eye tracking software, more accurate assessments of attention bias can be made, allowing researchers to examine how this cognitive bias might mediate the effect of genetic risk on outcomes such as depression and anxiety.

Secondly, due to the limited sample size, and further decline in numbers following the first wave, the current study was underpowered to detect effects that may well have been present. Furthermore, survival analysis highlighted that the retention rate for those with higher MDD PRS scores was slightly less than those with lower MDD PRS, although the difference was not significant. However, despite no significant differences, the loss of those with higher MDD PRS scores, that were likely playing a significant role in driving previous associations at wave one may have impacted on the associations at later waves. The initially small sample, and the impact of further reduction both in relation to higher MDD PRS score, and in general, likely impacted on several findings observed to be nominal that would likely have been significant following multiple testing correction in a larger sample with increased power. It is expected that with greater statistical power through an increase in sample size these limitations could easily be addressed, and that the true extent of associations observed in the current study will become evident.

Lastly, it was also not possible to assess the effects of cognitive biases on the development of anxiety due to anxiety symptoms seemingly being already embedded within the sample before the first wave. This was problematic as it was no longer possible to disentangle the relationship between the biases and anxiety and assess the developmental trajectory of anxiety through the

biases. With anxiety said to develop and express earlier than depression it is likely that measurements at earlier timepoints will help disentangle and assess this relationship.

5.4.4. Implications

The findings from the current chapter should be interpreted with care in light of the above limitations. However, despite this, there are a number of noteworthy implications regarding the current results that should be highlighted. Firstly, the current study has demonstrated for the first time that an adult clinically defined MDD PRS is associated, not just with depression and anxiety symptoms, but also cognitive biases in memory and social interpretation. This finding supports and extends on previous research (Eley et al., 2007; Eley et al., 2008) suggesting that the genetic aetiology of cognitive biases in memory and social interpretation overlap with that of depression and anxiety, as significant amounts of variance were explained by the MDD PRS. Furthermore, this also demonstrates that variants associated with clinical psychopathology in adulthood are also at play within and across symptoms of affective disorders and related phenotypes in late childhood and adolescents.

Secondly, and of great interest, the MDD PRS was shown as having the strongest association with the *positive* components of both memory and social interpretation biases, with the PRS showing nominally significant associations with a lack of both positively endorsed and recalled words in the SRET task, and the positive interpretation of social situations. This is particularly interesting as it suggests that a genetic risk for depression is likely related not to a negative bias, but rather a lack of a positive bias and, may have some important implication for how depression is conceptualised and treated. However, replication in a larger sample, with increased statistical power to detect such associations is required to validate the current findings.

Furthermore, these same cognitive biases in memory and social interpretation were shown to mediate the relationship between genetic risk and depression scores across waves suggesting in most cases a reciprocal relationship between these biases and later depression score. However, findings robust to the effects of reverse causality regarding memory bias as mediating the relationship between the MDD PRS and depression scores at later waves suggested a more causal relationship. This could suggest that those at genetic risk for depression may significantly benefit from CBM training at an early age in order to buffer against any genetic risk that may result in

depression later in life. Several recent studies have attempted to alter memory bias using CBM methods (Arditte Hall, De Raedt, Timpano, & Joormann, 2018; Eigenhuis, Seldenrijk, van Schaik, Raes, & van Oppen, 2017; Vrijsen et al., 2014). These studies, although in their infancy, provide evidence that training depressed individuals to have a more positive memory bias and hold on to less overgeneral memories can reduce rumination as well as symptoms of depression. These findings, along with the findings of the current study, could have serious implication for researchers and practitioners alike. However, further research is required to examine and validate whether positive bias training can significantly reduce the risk of depression *onset* in later life in those at high genetic risk.

5.4.5. Conclusion and future directions

This is the first time an adult MDD PRS has been used to predict depression and multiple cognitive biases within a sample of adolescents and show significant variance explained for biases in memory and interpretation as well as depression and anxiety. Furthermore, by using this approach the current study has identified stable genetic effects of the same MDD PRS overtime across adolescence, whilst also demonstrating the significant mediation of the relation between adult genetic risk and depression via memory and interpretation biases. It is clear that more research is required to replicate and validate these findings in an independent sample. However, as highlighted above there are several limitations that should be addressed in order to better understand the relationships demonstrated in the current study.

For instance, it is essential that issues regarding the measurement of attention bias are addressed in future research, either through the use of eye tracking software, or other such reliable means. Furthermore, as evident from findings regarding anxiety in the current study it is also imperative that future research considers measures at earlier periods of developments. This will aid in capturing both the cognitive biases and the psychopathologies before they become too embedded and/or entangled with one another.

Moving forward, it is also essential for future research to attain significantly increased sample sizes, and with it, greater statistical power to detect specific effects, such as factors that may be moderating these mediated associations. For example, similar studies with increased power will be able to examine whether the effect of positive and negative life events significantly

moderate the relationship between genetic risk for depression and biases in memory and social interpretation within these mediation models, something that the current study was underpowered to assess. Increased power will also allow for a more definitive assessment of how stable the effects of a PRS overtime are, as well as structural equation modelling in the form of cross-lagged mediation models. This will likely help in disentangle the relationships between cognitive biases, psychopathology and life events, and give greater insight as to whether these cognitive biases truly do lie on a causal pathway from genes to psychopathology. Once again, as mentioned in the previous chapter, gender specific differences in cognitive biases should also be examined in future studies that have achieved adequate statistical power to do so.

Extending on the methods used in the current study by including more and earlier timepoints, reliable measures of attention bias, and including both positive and negative life events from a scale with well-balanced, unambiguous and validated items will further build on the fields understanding of these prolific psychopathologies. Such future research will also likely provide much needed information regarding how best to design new and effective treatments and interventions.

6. Chapter 6: Discussion - Summary of what has been learnt about cognitive biases, genetic risk, psychopathology and wellbeing.

The basic premise of the CogBIAS hypothesis, outlined in detail in Chapter one (**Section 1.3.6**), suggests that the development of cognitive biases is at least partly responsible for outcomes of either psychopathology or wellbeing. Briefly, the hypothesis proposes that positive and negative cognitive biases develop as a result of positive and negative environmental effects, genetic variants that increase sensitivity to the environment, and the interaction between them. This is proposed to result in the development of either negative ("toxic") or positive ("enhancing") biases which in turn impact on psychological wellbeing. A further suggestion of the CogBIAS hypothesis is that cognitive biases may represent a mechanism through which differential susceptibility occurs.

The overarching aim of the current thesis was to test the assumptions proposed by the CogBIAS hypothesis. To do this, the thesis examined the developmental aetiology of multiple cognitive biases, their impact on normal daily life experiences, and their role as potential intermediate phenotypes driving differential effects on self-reported depression and anxiety. Study one (Chapter three) focused on the role of cognitive biases in response to daily life events in a sample of young adults. Study two (Chapter four), took a longitudinal approach to assess both genetic and environmental influences on the development of cognitive biases in adolescents. Study three (Chapter five), took a longitudinal whole-genome polygenic approach to assess whether genetic risk for psychopathology, and the emergence of symptoms over time, were mediated by cognitive biases in the same sample of adolescents assessed in study two. This chapter will summarize findings from each chapter and discuss the results in relation to the research question, specific components of the CogBIAS model, as well as their implications.

6.1. Summary of results

6.1.1. Chapter three: Study one: Cognition and Response to Environmental Stimuli (CRESt) - The effect of cognitive biases on affective states in response to daily life events

Previous research has demonstrated associations between cognitive biases and emotional reactivity (Fox et al., 2010; Clasen et al., 2013; LeMoult), and reward sensitivity and affective states (Hundt et al., 2013) in response to stress. In turn, stressful or negative life events have also

been shown to be associated with increased risk for depression and anxiety (Allen et al., 2008; Goodyer et al., 1990; Williamson et al., 2005). The CogBIAS hypothesis suggests that positive ('enhancing') or negative ('toxic') cognitive biases, once established, may result in subsequent information processing becoming skewed in accordance with the bias. This skewed processing is then likely to reinforce heightened sensitivity to either positive or negative environmental influences depending on the nature of the bias. Whilst a positive bias is proposed to increase wellbeing and resiliency, a negative bias will likely, in combination with other factors, eventually lead to the development of negative affective states and disorders. This is the first element of the CogBIAS hypothesis that was tested in the current thesis and is illustrated in **Figure 6.1**.

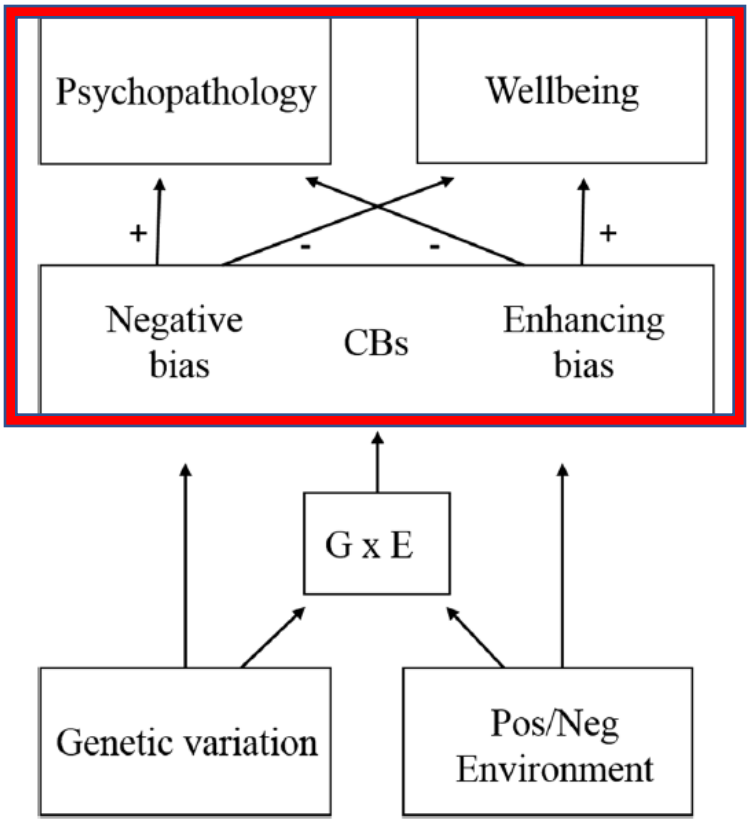


Figure 6.1. The CogBIAS model as originally proposed by Fox and Beavers (2016). The red box illustrates what specific aspects of the CogBIAS hypothesis were tested in study one.

In order to assess this component of the model, a smartphone ESM application was designed to continually gather information regarding response to daily life events across seven days. This application was then used to assess whether cognitive biases in interpretation and

memory, measured prior to seven days of experience sampling, were associated with positive (rewarding) and negative (stressful) affective mood states in daily life.

In support of the hypothesis, and to some extent the specific aspect of the CogBIAS hypothesis under examination, cognitive biases, particularly a negative bias in interpretation, was shown to be associated with lower daily life levels of Positive Affect (PA). However, no significant associations were found between any of the cognitive biases and Negative Affect (NA). Furthermore, daily levels of PA and NA were not shown to significantly vary as a result of cognitive biases in either memory or interpretation. Results regarding the effect of cognitive biases on the perceived quality of daily life contexts did however demonstrate that interpretation bias was significantly associated with the perceived quality of a previous event, and nominally associated with perceived quality of the current activity. Both had negative effects, with the significant association between interpretation bias and the perceived quality of a previous event suggesting that a more negative interpretation bias reduced the perceived enjoyment of the previous event. Interaction analysis examining the moderating effects of cognitive biases on affect reactivity to daily life contextual events also revealed multiple significant associations regarding interpretation bias. Specifically, a negative interpretation bias significantly moderated the effects of positive previous events and positive current activities to reduce levels of PA, buffering against the positive effects of both environmental contexts. Furthermore, and of particular interest, a negative interpretation bias also moderated the effects of both positive solitude (alone by choice) and negative solitude (not alone by choice), resulting in an increase in both PA and NA respectively. However, further analysis revealed that the result regarding a negative interpretation bias moderating the effect of negative solitude on NA was not robust.

6.1.2. Chapter four: Study two: The development of cognitive biases: The effect of candidate sensitivity variants and positive and negative life events

Research demonstrates that the aetiology of cognitive biases has both genetic and environmental components (Anokhin et al., 2010; Eley et al., 2007; Eley et al., 2008; Lau & Eley, 2008; Lau et al., 2006; Rijsdijk et al., 2009; Silverman et al., 1999; Stein et al., 1999; Weinberg et al., 2014) with the interaction between these components also significantly impacting on their development (Fox et al., 2011; Jenness et al., 2016; Johnson et al., 2010; Stein et al., 2008; van Oostrom et al., 2012). Furthermore, many of the genetic variants and environments associated with

cognitive biases have also been implicated in depression and anxiety (Bukh et al., 2009; Caspi et al., 2003; J Chen et al., 2012; Elovainio et al., 2007; Gunthert et al., 2007; Hosang et al., 2014; Mandelli et al., 2007; Zimmermann et al., 2011). The CogBIAS hypothesis suggests, much like with any complex trait, that cognitive biases such as those observed in attention, interpretation, and memory are the result of both genes and the environment, as well as the interaction between them (Fox & Beevers, 2016). Specifically, it is suggested that genetic variation increases sensitivity to environmental effects, which then lead to the development of either negative or positive ("enhancing") biases depending on the quality of the environment. This aspect of the CogBIAS hypothesis was tested in study two (chapter four) is illustrated in **Figure 6.2.**

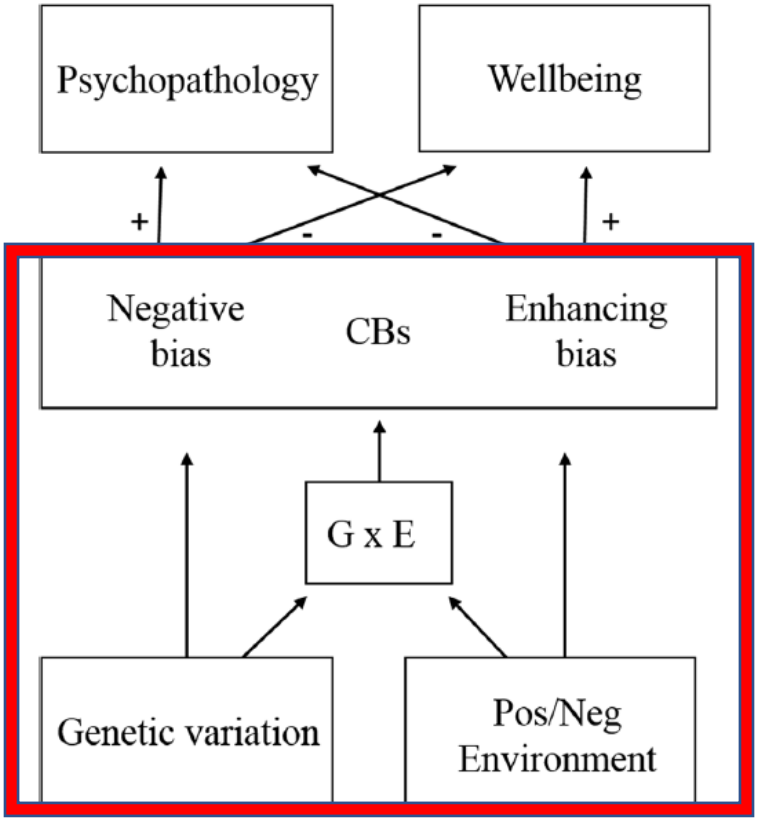


Figure 6.2. The CogBIAS model as originally proposed by Fox and Beavers (2016). The red box illustrates what specific aspects of the CogBIAS hypothesis were tested in study two.

In this chapter, longitudinal data from the CogBIAS-L-S was used to assess the role of 28 candidate variants implicated in environmental sensitivity by previous GxE research, on the development of cognitive biases in adolescents across three timepoints. The effects of each variant

were assessed independently, collectively as part of a combined candidate sensitivity score (CSS), and in interaction with positive and negative life events.

In line with the hypothesis for study two and the CogBIAS hypothesis more broadly, negative life events were significantly associated with negative biases in memory, and interpretations of social and non-social scenarios, while positive life events were associated with positive biases in memory and interpretations of social scenarios across the three timepoints. Findings regarding the effect of positive life events on cognitive biases, but not negative, were robust to sensitivity analysis which excluded any events found to be influenced by a reporting bias due to pre-existing cognitive biases. However, the significant effect of negative life events on the negative memory and social interpretation bias components (negative endorsed and recalled and negative social interpretation respectively) remained, as did the effects of positive life events on the positive memory bias component (positive endorsed and recalled). Further sensitivity analysis, excluding events influenced by a reporting bias and those shown to be dependent on an individual's behaviour, demonstrated the association between negative life events and negative endorsed and recalled as a robust finding, and the only to survive both phases of sensitivity analysis, following correction for multiple testing.

Furthermore, and also in keeping with the hypothesis, the candidate sensitivity score (CSS) had a significant positive main effect on a social interpretation bias, increasing a negative interpretation of social scenarios. However, this effect was driven by a negative main effect on the positive social interpretation bias component (positive social interpretation), reducing a positive interpretation of social scenarios. The CSS also significantly moderated the effects of negative life events on non-social interpretation bias and positive life events on memory biases. Whilst the effect of negative life events increased a negative interpretation bias of non-social scenarios in those with a high CSS, the effects of positive life events were shown to reduce a negative memory bias only in those with a low CSS. However, the CSS-by- negative life events on interaction on non-social interpretation bias was not robust to either phase of sensitivity analysis and was also confounded by depression and anxiety symptoms. This was not the case for the CSS-by-positive life events interaction on memory bias as it was robust to reporting bias but was likely driven in part by life events dependant on an individual's behaviour.

Associations were also found between several of the 28 individual sensitivity variants and cognitive biases. Two variants, rs110402 in CRHR1 and rs1049353 in CNR1, had a significant positive and negative main effect, respectively on social interpretation biases, both surviving correction for multiple testing. Significant genotype-by-time interactions were demonstrated for variants rs2242446 in SLC6A2 on memory bias, and rs6313 and rs6311 in HTR2A on negative non-social interpretation, both significantly reducing a negative bias. There was also strong evidence for significant gene-by-negative life event interaction effects of rs6265 in BDNF increasing a negative memory and non-social interpretation bias, as well as the reducing the positive memory bias component (positive memory bias) in minor allele carriers. These effects were also shown in the same variant-by-positive life events interactions. However, here the effect was shown to reduce a negative memory bias and increase the positive component of memory bias (positive memory bias) in major allele homozygotes. Furthermore, a similar effect was observed for rs1800497 in DRD2-by-positive life events increasing the positive memory bias component (positive endorsed and recalled) in major allele homozygotes. Only the interaction between rs6265 and negative life events on non-social interpretation bias remained robust to the effects of reporting bias following correction for multiple testing. All other variant-by-life events interactions were robust to the effects of reporting bias following multiple testing corrections.

Of particular interest, the effects of depression and anxiety were found to be broadly specific to the effect of negative, but not positive life events. That is, all main effects of negative life events on cognitive biases and their components, with the exception of the negative memory bias component (negative endorsed and recalled), were confounded by depression and anxiety symptoms. This was also true for the effect of the CSS-by-negative life events on non-social interpretation bias, but not for the effect of the CSS-by-positive life events on memory bias which showed little change. Elsewhere, whilst the main effects of the CSS on social interpretation bias and its positive component (positive social interpretation) remained, the effect of both CRHR1 (rs110402) and CNR1 (rs1045393) on memory bias were found to be confounded by depression and anxiety. All candidate sensitivity variant-by-time and by-life event remained robust to the effects of depression and anxiety, with findings involving negative life events seeing a drop in effect, whilst those involving positive life events saw little change.

6.1.3. Chapter five: Study Three: Cognitive biases as potential mechanisms mediating genetic risk for depression and anxiety: A phenome-wide polygenic approach.

Polygenic risk scores (PRS) have been shown to predict both depression and anxiety (Demirkan et al., 2011), with further studies also demonstrating that PRSs for one disorder can predict variance in other disorders and phenotypes (H. J. Jones et al., 2016; Mistry et al., 2018; M. G. Nivard et al., 2017). Therefore, the development of one behavioural phenotype or disorder, once established, could mediate the development of other more serious psychopathology later in life due to shared genetic architectures. This has been demonstrated longitudinally to some extent in children, adolescents and adults with phenotypes such as attribution style (Lau & Eley, 2008), and neuroticism and resilience (Navrady et al., 2018), mediating later depression and anxiety. The CogBIAS hypothesis suggests that variations in cognitive biases may mediate the effects of genetic risk for affective disorders, and, hence, that such biases could represent targets for new behavioural treatment and interventions, vital to improving efficacy, and better treat such disorders. This proposed effect was tested in study three (chapter five) and illustrated in **Figure 6.3.**

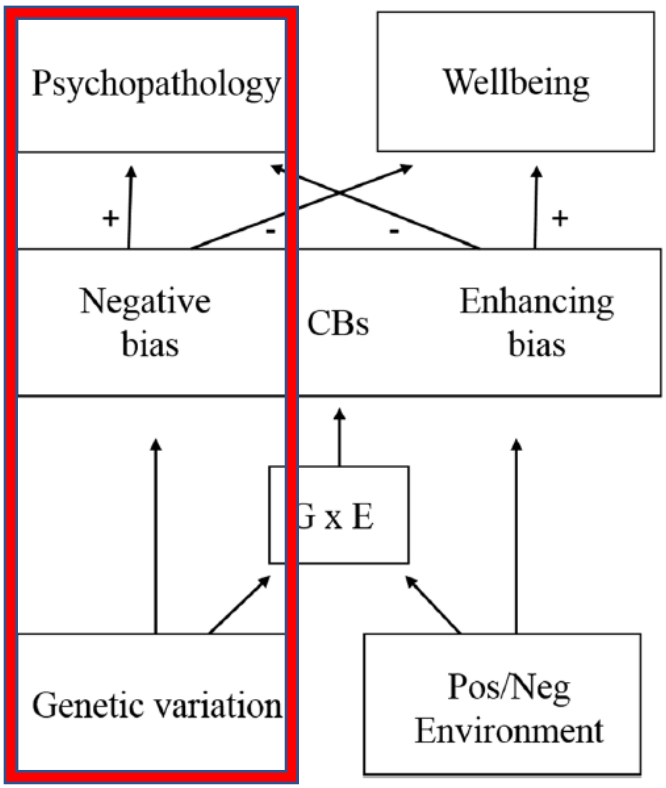


Figure 6.3. The CogBIAS model as originally proposed by Fox and Beavers (2016). The red box illustrates what specific aspects of the CogBIAS hypothesis were tested in study three.

A polygenic phenome-wide approach was used in study three (chapter 5) to assess, using a longitudinal design, whether the relationship between an adult MDD PRS and depression and anxiety symptoms, within the adolescent CogBIAS-L-S sample, was associated with, and mediated by cognitive biases.

In line with an assumption regarding the CogBIAS hypothesis and that of study three (chapter five), an adult MDD PRS was demonstrated as having a significant main effect on both depression and anxiety symptoms in the adolescent CogBIAS sample. Furthermore, the same MDD PRS was also shown as having a significant positive main effect on cognitive biases memory and social interpretation bias, increase negative biases in both cases. Of particular interest, it was demonstrated that a significant negative main effect of the MDD PRS on the positive components of memory bias (positive endorsed and recalled) and social interpretation bias (positive social interpretation), that were significant following multiple testing corrections, were driving the association with these biases. The effect of the MDD PRS on anxiety and the cognitive biases remained stable across time. However, for depression the MDD PRS-by-time interaction showed some evidence of change across time, with depression symptoms showing a nominally significant increase, although this was only seen at a single p-value threshold (0.01).

Cross-sectional analysis demonstrated several nominally significant associations between the MDD PRS and increased depression scores across each wave, with the strongest associations in wave two at thresholds 0.01 and 0.05 explaining up to 3.01% of variant in depression. The MDD PRS was also associated with increased anxiety explaining 4.96% of variance at threshold 0.01 of the same wave as well as increased negative memory and social interpretation bias explaining 3.88% and 3.28% of variance at the same wave and threshold respectively. The cross-sectional analysis also revealed a shift in the effects of positive and negative components driving associations between the MDD PRS and cognitive biases in memory and social interpretation bias wave two. The MDD PRS was significantly associated with an increase in negative components of these biases (negative endorsed and recalled and negative social interpretation) explaining 2.90% and 2.23% respectively, compared with 1.53% and 1.80% of their respective positive counterparts. However, it is important to note that associations with the positive components were far more consistent across the three waves and that there was a drop in the retention rate across each wave to which cross-sectional analysis is not robust. Furthermore, despite this spike in association with the negative components of these biases at wave two, it was a lack of the positive

components that remained the driving force behind the associations between the MDD PRS and both memory and social interpretation bias at wave one and three.

Mediation analysis revealed memory and social interpretation bias and their positive components as significant partial mediators of depression, but not anxiety. However, whilst the mediating effects of social interpretation bias were consistent across each and all waves, it was memory bias that had the strongest mediating effect. Furthermore, there was evidence for reverse causality regarding the effects of social interpretation bias at wave two mediating depression scores and wave three. This was demonstrated as the inverse relationship between the MDD PRS and social interpretation bias at wave three was also significantly mediated by depression at wave two. However, there was robust and reliable evidence that memory bias at wave one mediated genetic risk for depression on depression scores at both wave two and wave three. This was evident, as whilst inverse mediation of these effects did highlight a reciprocal relationship between memory bias and depression symptoms, this was not due to reverse causality. That is, the MDD PRS, whilst having a direct association with memory bias at wave two and three, was not significantly associated with depression at wave one, and therefore did not mediate the relationship between the MDD PRS and memory bias.

6.2. Genes, environments, cognitive biases and psychopathology: Is there support for the CogBIAS Hypothesis?

Overall, despite some caveats, the findings from the current thesis support several aspects of the CogBIAS hypothesis. Firstly, the notion that an established negative cognitive bias increases risk of psychopathology was supported by study one (chapter three) as a negative interpretation bias was shown to reduce PA over time, and also moderated the effects of environmental context, as it buffered against positive environmental effects. Furthermore, the assumption that a negative cognitive bias skews subsequent information processing was also supported by study one (chapter three), as a negative interpretation bias significantly reduced the perceived enjoyment of past events. Secondly, in study two (chapter four), it was shown that cognitive biases in interpretation and memory develop over time as a result of variations in specific genetic variants that increase sensitivity to environmental effects, positive, and negative environments, and the interaction between them. Finally, study three (chapter five), using an MDD PRS, provided evidence that cognitive biases in social interpretation and memory share a genetic architecture with depression.

Furthermore, study three (chapter five) supported the suggestion that a negative cognitive bias (memory bias) precede and robustly mediate the development of psychopathologies, in this case depression.

Despite these findings that provide some support for the CogBIAS hypothesis, there were also some elements that could not be confirmed either due to a specific aspect of the study design or simply because evidence of such an effect was not observed, or observed in the opposing direction. The following section highlights these issues, as well as some specific fundamental issues with the current CogBIAS model, as demonstrated by findings from the current thesis, and in turn the need for specific amendments to be made.

The design of study one (chapter three) did not allow for the assessment of psychopathology and wellbeing directly, focusing instead on changeable affective states as is a common practise in ESM studies. Therefore, it was also not possible to conclude that cognitive biases lead to wellbeing or psychopathology, but only to mood states that increase likelihood of both. Furthermore, an unexpected finding demonstrated a robust positive moderating effect of negative interpretation bias on PA in the environmental context of positive solitude. Whilst associations between other positive contexts and outcomes were buffered against by the presence of a negative interpretation bias, choosing to be alone for those with a negative interpretation bias had beneficial effects for levels of PA. This finding was in direct contrast to that proposed by the CogBIAS hypothesis, as it would be expected that a negative interpretation bias would skew cognitive processing and buffer against such environmental effect, as it did with the other significant findings regarding positive environmental contexts. This suggests that the effects of a negative interpretation bias in certain environmental contexts are not as straight forward and consistent with the proposed CogBIAS hypothesis, possibly having more adaptive function, and not always resulting in detrimental outcomes. Therefore, it may be that those with such a negative bias require a differential set of environments/treatments to those with more positive biases to actualise positive outcomes. If so, this would implicate the need to assess the effect of specific biases and environments in greater detail and build a more flexible model to allow for such differential effects.

In study two (chapter four) the significant CSS-by-positive life events interaction on memory bias was not found to be in a direction consistent with either Differential Susceptibility

or the CogBIAS hypothesis. That is, whilst this finding did confirm the broader proposal that variations in genetic effects combined with variations in environmental factors do impact on the development of cognitive biases, it was the genetically less sensitive group that benefited most from positive life events, with the more sensitive group showing little change. This suggests that the genetic load specific to those variants included in the CSS on positive and negative memory bias seems only to be evident in the presence and absence of positive life events, and only in those without the sensitivity alleles. This interaction was therefore more in keeping with Vantage Sensitivity and brings into question the selection, or possibly the coding of the selected candidate sensitivity variants. For example, allelic variations across the selected candidate sensitivity variants were shown as increasing sensitivity to either positive life events (Vantage Sensitivity), or to a lesser extent negative life events (Diathesis Stress), rather than a specific allele increasing sensitivity to both (Differential Susceptibility). Whilst there were significant interactions regarding the individual candidate sensitivity variants (particularly rs6562 in BDNF) and both positive and negative life events on cognitive biases, it is important to note that genetic variants do not act in isolation. Nevertheless, these patterns of interactions, particularly with regards to rs6562, remained in keeping with either Vantage Sensitivity or Diathesis Stress, further supporting the hypothesis that the selected candidate sensitivity variants were not general sensitivity variants. Therefore, the current thesis cannot support or refute that cognitive biases represent a mechanism through which differential susceptibility occurs as the selected variants were likely not associated with general sensitivity. However, findings have provided some evidence to suggest that cognitive biases may represent a mechanism through which Vantage Sensitivity and to some extent Diathesis Stress occurs. This is in keeping with the CogBIAS hypothesis suggesting that variants that increase sensitivity to positive or negative environmental effects, also increase positive or negative cognitive biases in the presence of adverse or beneficial environments respectively. However, it is thought that the CogBIAS model would benefit from incorporating multiple pathways that more clearly differentiate between GxE interactions regarding Vantage Sensitivity, Diathesis Stress and Differential Susceptibility. This would likely make for a more nuanced model for understanding the development of cognitive biases and psychopathologies.

A further issue, highlighted in study two (chapter four), and relevant to the CogBIAS hypothesis was the association between specific types of life events, particularly regarding their vulnerability to reporting bias due to existing cognitive bias, and whether they were dependant or

independent on an individual's behaviour. Although dependant and independent life events do not segregate in real-life scenarios, both are clearly important factors in the development of cognitive biases and separating out their effects becomes necessary when attempting to understand these effects accurately. This is particularly true as many of the significant findings from study two were found to be, in part, driven by the effects of such dependant life events. This suggests that it becomes important for the CogBIAS hypothesis, when using such life events scales, to incorporate the potential for variations in the direction of causality as responses to items regarding ambiguous life events that are open to interpretation, and those dependent on an individual's behaviour may lead to false positive findings. However, this may be far too complicated to successfully implicate, and it is important to reiterate that the loss in significance regarding the independent life events list may have also reflected the substantial drop in statistical power due to the removal of over two thirds of the original 38 items. An additional solution to this problem, as touched on in study two (chapter four), would be for any further assessment of the CogBIAS hypothesis, or future iterations, to use a method of assessing life events that is free of ambiguity, with prefixed severity ratings and balanced in terms of dependant and independent life events.

Study two (chapter four) also demonstrated that the confounding effects of psychopathologies depression and anxiety were widely specific to the effects of negative life events but not positive life events. This finding, whilst being particularly interesting, also has important implications for the current CogBIAS hypothesis as it suggests that the relationship between negative life events and negative cognitive biases are dependent on depression and anxiety symptoms. This is in direct contrast to the proposal of the CogBIAS hypothesis as this would in turn suggest that depression and anxiety symptoms play a significant role in the development of such negative cognitive biases. Conversely, the effect of positive life events on the absence and presence positive cognitive biases, and in some cases on negative biases (CSS-by-positive life events on memory bias), were independent of the effects of depression and anxiety. If replicated this may suggest the need to amend the current model accordingly, to reflect the importance of both the absence and present of positive life events, both as main effects, and when interacting with genetic variants on the development of both negative and positive cognitive biases. Furthermore, this would also require the effects of negative life events on negative cognitive biases to be reconceptualised as not preceding psychopathology but representing a potential by-product of depression and anxiety symptoms. Whilst it was the case that the effects of negative life events

on the negative memory bias component (negative memory bias) survived sensitivity analysis using both the 19-item and 11-item CASE and was robust to the effects of depression and anxiety, it was not enough to drive a significant effect on memory bias itself. Furthermore, it was the only finding regarding negative life events to survive the effects of these psychopathologies, standing apart from all findings regarding the main effects of negative life events and possibly suggesting that this finding was significant only by chance. However, only an attempt at replicating this finding will be able to confirm this speculation.

The findings in study three (chapter five) provided important evidence for the absence of a positive and not the presence of a negative bias as being significantly associated with a genetic risk for depression. This echoed the findings in study two (chapter four) regarding the significant association between the CSS and social interpretation bias, driven not by its negative component, but by an absence of its positive component. In terms of the CogBIAS hypothesis, these implications have particular importance as it suggests that only the positive components of cognitive biases have a genetic basis whilst the negative components maybe more environmentally driven. Furthermore, associations between genetic risk for depression and the positive components dropped from wave one to wave two as associations with depression scores increased. This could suggest that the genetic effect on the positive components of cognitive biases are somewhat dynamic, behaving in a transdiagnostic fashion and moving, in this case, from an absence of a positive bias to an increase in depressive symptoms. This could also implicate a fundamental difference between the positive and negative components of cognitive biases not currently conceptualised in the CogBIAS hypothesis. Taken together, the absence of a positive bias may be far more important to the development of both negative cognitive biases and in turn psychopathology when compared to the presence of a negative bias. The CogBIAS hypothesis does not make the possibility of this effect clear in the current model, seeming to suggest only that, in combination with other factors, negative biases increase risk of psychopathology, and positive (or "enhancing") biases increase resilience and positive affective states. In light of the current findings, and if replicated, this would suggest that the current CogBIAS model would need to be amended to reflect positive and negative biases as not simply the opposing ends of the same scale but instead representing separate phenotypes with distinct dimensions and effects.

Study three (chapter five) also demonstrated significant mediation effects of genetic risk for depression by memory bias on depression scores at later timepoints and highlighted a reciprocal

relationship between memory bias and depression symptoms. Whilst results were robust to reverse causality suggesting that the bias precedes a build in depression symptoms, a reciprocal feedback loop maybe required in the current model to highlight the possibility of this effect.

The findings and their implications discussed above provide support for the CogBIAS hypothesis whilst also highlighting some potentially important amendments that may need to be included to increase the model reliability, especially if they are replicated. However, since the completions of the research towards the current thesis, the CogBIAS hypothesis developed by Fox and Beevers (Fox & Beevers, 2016), and tested throughout the three empirical chapters, has been updated (Fox & Keers, 2019), and is illustrated below in **Figure 6.4**.

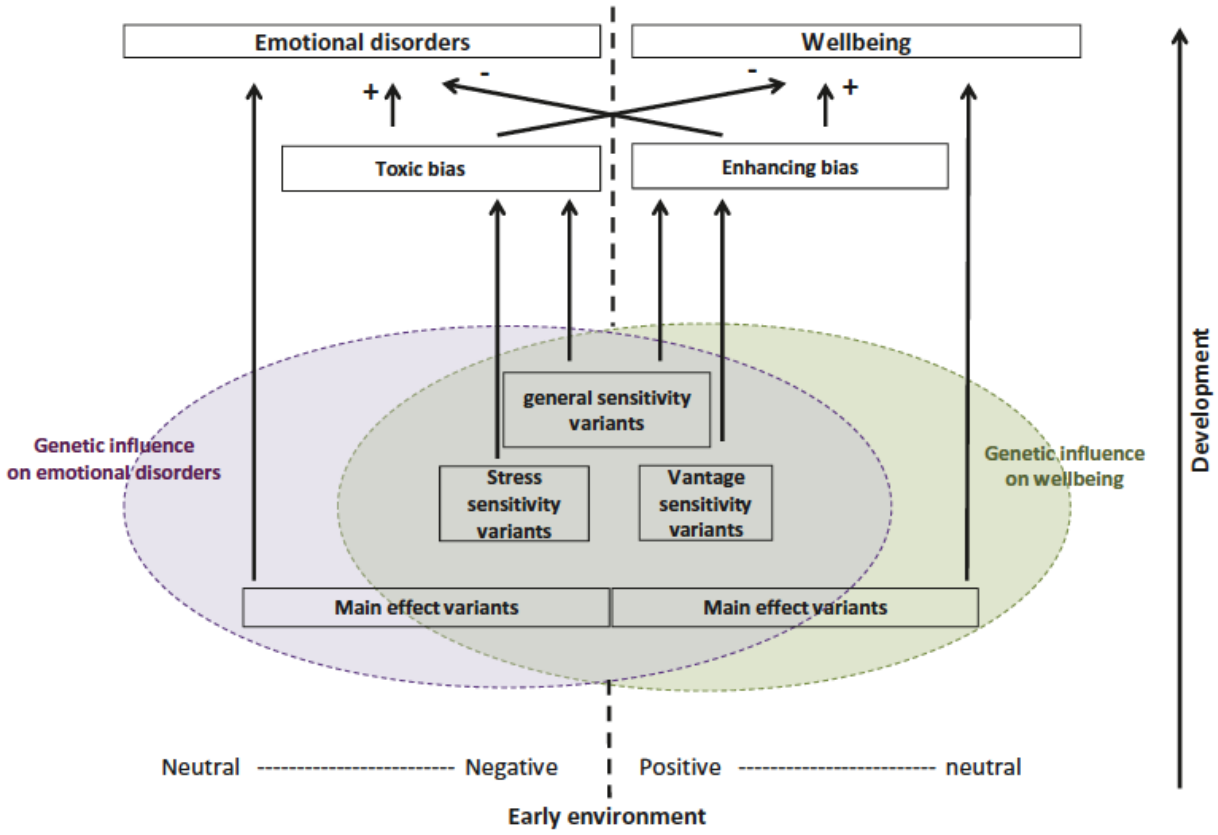


Figure 6.4. The Updated CogBIAS model (Fox and Keers, 2019).

The central hypothesis remains mostly unchanged, suggesting that biases in cognitive processing could potentially lie on a causal pathway between the effects of genetic factors and psychopathology or wellbeing. However, in keeping with a suggestion made above, this updated CogBIAS model has incorporated more nuanced pathways now clearly differentiating between

specific types of genetic variants in terms of potential GxE interactions. Specifically, those impacting stress sensitivity ('stress sensitivity variants'), those that influence response to positive environments ('Vantage-Sensitivity variants'), and those that increase general sensitivity ('general-sensitivity variants'). A further addition is the direct, main effect pathway from 'main effect variants' to either emotional disorders or wellbeing.

The updated hypothesis proposes that the effect of variants, in keeping with the distinctions made in the model, impact on cognitive biases, emotional disorders, and well-being in the context of neutral-negative and neutral-positive early environments. The remaining hypotheses vary little from the original model aside from direct pathways concerning main effect variants not being mediated by cognitive biases. That is, 'vantage sensitivity variants' are expected to lead to enhancing cognitive biases in the context of positive early environments, 'stress sensitivity variants' are expected to lead to toxic cognitive biases in the context of negative early environments, and 'general sensitivity variants' are expected to lead to either enhancing or toxic biases depending on the context of early environments.

This new, more nuanced iteration of the CogBIAS hypothesis has incorporated one of the suggestions made above regarding a clearer distinction between GxE interactions. However, the update model may also need to consider other suggested amendments discussed above if current findings are replicate. These include,

1) a further distinction regarding the types of life events (ambiguous, dependent and independent),

2) the potential confounding relationship between psychopathology and negative life events, and the unconfounded relationship between a lack of positive life events on negative cognitive biases,

3) the adaptive functions and potential benefits of specific negative cognitive biases in specific environmental contexts,

4) the impact regarding an absence of a positive cognitive bias components on increased negative cognitive biases,

5) the inclusion of a reciprocal feedback loop following mediation by cognitive biases on psychopathology.

However, whilst the current thesis has potentially provided evidence for cognitive biases as a mechanism for GxE pathways regarding 'vantage sensitivity variants' and 'stress sensitivity variants', the 'general sensitivity variants' pathway is yet to be accurately assessed. Furthermore, the associations demonstrated in the current thesis require similar rigorous testing in a considerably larger sample to both confirm these findings and further test the new updated CogBIAS hypothesis.

6.3. Strengths and limitations

Notwithstanding the wider strengths of the current thesis, including the use of a longitudinal study designs, genome-wide and ESM approaches, there were also several other important and novel strengths that should be noted. For example, the current thesis represents the first time that multiple cognitive biases have been assessed longitudinally within the same study. Additionally, the assessment of both positive and negative cognitive biases, their respective components and, in study two (chapter four), the assessment of both positive and negative life events provided additional novelty and strength to the current thesis. Furthermore, whilst separate cognitive biases, genes and life events have in the past been assessed in relation to depression and anxiety, this has classically been done in separate lines of research. Therefore, the research presented throughout the current thesis also represents the first time that such cognitive, genetic and environmental theory has been integrated and assessed within empirical study designs.

Other more specific strengths include the use of an adult MDD PRS to assess potential intermediate phenotypes for the depression and anxiety in a child sample. This novel approach statistically increased the longitudinal range of the study and demonstrated the potential of such an approach for future research. Lastly the thorough dissection of the life event scale used, further examination of interactions using simple slope analysis, and sensitivity analysis regarding the effects of psychopathologies and separated life event types gave increased validity to the current findings. However, despite these strengths, finding across the current thesis should also be interpreted in light of several methodological limitations. Whilst many limitations which were specific to each of the study chapters have already been discussed, the following section will discuss the specific issues relating to the measures of cognitive biases which were consistently evident across all study chapters.

A key limitation of the current thesis was the use of the dot-probe task as a measure of attention bias, as it was found to be an unreliable measure of attention bias in all three empirical

study chapters and in the CogBIAS project generally (Booth et al., 2019). This unfortunately resulted in the current thesis being unable to assess the development of attention bias through genetic and environmental influences, its effects on levels of affect in response to daily life, and as mediating genetic risk on depression and anxiety. Therefore, it was not possible to confirm or refute the extensive amount of previous research that has assessed attention biases, or whether it fits within the framework proposed by the CogBIAS hypothesis. Eye tracking software, has been successfully implemented in several studies (Beevers, Ellis, Wells, & McGeary, 2010; Beevers et al., 2011; Gross, 2014), and may represent a much more reliable and replicable way of measuring attention biases as it allows for continuous motoring of visual attention. It can therefore measure attentional focus throughout the entire time stimuli are present, rather than relying on reaction time to separate stimuli, which may not alone, represent an accurate measure of attention bias.

Furthermore, it could also be argued that the SRET used for the measure of memory bias, despite being an established measure, is not a complete measure as it assesses only explicit memory which involves conscious and intentional processing of factual information and does not include a measure of implicit memory. Although not as consistent as research examining explicit memory, some supporting evidence has been provided for implicit memory bias in depression (Bradley, Mogg, & Millar, 1996; Ruiz-Caballero & González, 1997; Taylor & John, 2004; P. C. Watkins, Martin, & Stern, 2000; P. C. Watkins et al., 1996). Described as a type of long-term memory not subject to conscious thought or any intentional effort (Graf & Schacter, 1985), implicit memory bias is defined as the tendency to recall or recognise emotional stimuli without having had the intention to retain the information or the emotional content attached to it. Therefore, implicit memory bias could represent an important addition to the measure of memory bias as it is not exclusively influenced by deliberate recall. Whilst the findings from the current thesis regarding memory bias remain significant and of particular interest it is thought that the full effect may not have been captured, and that a measure implicit memory could potentially enhance these findings.

6.4. Implications

Despite the limitation discussed above, and those particular to each of the study chapters, the current thesis has demonstrated several novel effects that could represent steps towards further understanding the relationship between cognitive biases and affective states and consequent disorders. Again, aside from the more specific implications highlighted in detail in each of the

study chapters, there were also more overarching implications related to the thesis as a whole, with particular relevance for future cognitive bias research, as well as prevention and treatment strategies regarding associated disorders. These implications will be discussed below in the following sub-sections.

Despite there being several suggested amendments for the CogBIAS hypothesis, the current thesis has demonstrated the impact of cognitive biases on affective states and provided evidence for cognitive biases as potential intermediate phenotypes for affective states and potentially elements of psychopathology. These findings hold important implications for current, as well as the development of new treatment and intervention strategies for both affective states and disorders. For instance, whilst study one (chapter three) demonstrated that a negative bias can have detrimental effects on the level of PA throughout the course of daily life, and buffer against the effects of positive daily life contexts, it was also shown that particular environmental contexts can increase PA in those with negative biases. The benefits of positive solitude (choosing to be alone) for those with a negative interpretation bias provides an interesting avenue for research into targeted interventions for those with negative interpretation biases at risk of developing affective states and disorders. It could be suggested that quiet introspection, or activities and hobbies performed when alone may be of particular benefit to those with negative interpretation biases. Further research could examine this and other common daily environmental contexts that may benefit those with more negative interpretation biases to increase levels of PA by selecting themselves more frequently into such environments.

The findings from study two (chapter four) demonstrated that the effect of negative life events on negative cognitive biases are likely a result of depression and anxiety whilst the effect of positive life events on positive and negative cognitive biases are not. It may be that psychopathologies such as depression and anxiety increase the likelihood of experiencing life events as negative, and in turn also increase a negative cognitive bias that could potentially contribute to the maintenance of such psychopathologies. In contrast, the effect of positive life events on positive and negative cognitive biases demonstrates a potential developmental pathway, with and without the involvement of genetic variants, and unconfounded by the effects of depression and anxiety symptoms. Furthermore, study three (chapter five) also demonstrated an MDD PRS as being consistently associated with a lack of the positive components of both memory and social interpretation biases and driving associations with the biases themselves. Taken

together, this suggest that the positive components of cognitive biases, associated with genetic variants for affective disorders, and driving the development and maintenance of negative cognitive biases may be an important factor in the development of depression. This suggestion is supported by evidence that memory bias significantly and robustly mediated the relationship between the MDD PRS and later depression scores. Such robust associations between a lack of positive biases and depression may also have wider implications, potentially going some way to explaining the development of anhedonia, which is often present in, and a core symptom of depression. This has important implications for both the prevention and treatment of such disorders, as training aimed at increasing a positive bias rather than reducing a negative bias could result in far better treatment efficacy. Furthermore, if it is only the positive components of cognitive biases that share their genetic architecture with affective disorders, such positive bias training may have important protective effects. For example, as highlighted in study one (chapter three), cognitive bias modification techniques have shown that an increase in positive interpretation bias can increase levels of PA and reduce levels of NA. Building on this, the findings from the current thesis suggest that such an approach is likely also buffering against potential genetic susceptibility for low positive bias and an increased risk of developing a more severe disorder in the future. Taken together, this highlights the importance of such approaches for research purposes and as potential prevention and treatment strategies for such disorders and affective states. Lastly, given that study three (chapter five) also demonstrated that an adult polygenic score for MDD was associated with the development of cognitive biases as early as 12 years of age, and likely younger, this thesis also highlights that this developmentally sensitive periods may represent a very important time for such targeted treatments. However, there is still need for further assessment and replication before such findings can be effectively used in treatment and intervention programs. Despite this, given the current findings, and past research demonstrating associations between selective cognitive processing and emotional wellbeing (Mathews & MacLeod, 2005a), as well as differential effects of cognitive intervention (Fox et al., 2011), there is also ample evidence to suggest that such investigation represents an important area for future study.

6.5. Future directions

The findings of the current thesis require replication in independent samples as this is the first time that many of these effects have been demonstrated. However, such future research should also consider taking into account the limitations highlighted above, as this will likely provide further validity and reliability to future findings. For example, it is imperative future research accurately assess attention bias using a reliable measure such as eye tracking. Studies that have used this method to assess attention bias have demonstrated that depressed individuals have difficulty disengaging their attention from negative material (Caseras, Garner, Bradley, & Mogg, 2007; Eizenman et al., 2003), that this difficulty is associated with more maladaptive responses to stress (Sanchez, Vazquez, Marker, LeMoult, & Joormann, 2013), and that depressed participants differ from healthy control participants in the way they process positive information (Kellough et al., 2008). This method of measuring attention bias will likely prove to be vastly more reliable, valid and replicable than the dot-probe task. However, it is also important to acknowledge that whilst eye tracking represents a more accurate and reliable measure of attention bias, the dot-probe task, which is a well-established procedure, was likely chosen as it can be conducted both in lab and off site without the inclusion of the extra software and hardware needed for eye tracking. Therefore, the challenge becomes how to get such high quality and labour-intensive measures for a sample that is large enough to investigate genetic associations.

The absence of an implicit measure of memory bias in the current thesis is also an important factor to be addressed in future research. Previous research has shown, in line with cognitive theories of depression, that individuals with depression tend to exhibit a tendency towards implicit memory for negative rather than positive information (Bradley et al., 1996; Ruiz-Caballero & González, 1997; Taylor & John, 2004; P. C. Watkins et al., 2000; P. C. Watkins et al., 1996). Further research has also demonstrated that individuals with a history of depression have better memory for negative rather than positive stimuli using an incidental recall task (Vrijsen et al., 2014). Future research should consider assessing both explicit and implicit memory, as implicit memory clearly represents an important components of memory bias. This would likely provide a more complete understanding of the development and effects of memory bias, whilst also allowing for comparisons to be made regarding their impact on resilience and the development of psychopathology.

Furthermore, future research examining associations between cognitive biases and life events on affective disorders, such as depression and anxiety, should consider assessing life events in the context of the disorder(s) of interest. For example, previous research has demonstrated the effects of particular types of event as specifically associated with either depression or anxiety (Eley & Stevenson, 2000; Finlay-Jones & Brown, 1981; K. S. Kendler, Hettema, Butera, Gardner, & Prescott, 2003). For instance, in a study by Finlay-Jones and Brown (1981) examining a sample of 164 adult women, it was demonstrated that events involving elements of loss were specifically associated with the onset of depressive disorders, whilst those involving threat of future danger were specifically associated with the onset of anxiety disorders. In keeping with these findings, this pattern of association was also reported in a later child twin study of 61 twin pairs (Eley & Stevenson, 2000). Here researchers demonstrated that events relating to loss, schoolwork stress, and friend and family relationship problems as specifically associated with depression, whilst those related to threat were specifically associated with anxiety.

Additionally, more recent research has begun to highlight the importance of assessing phenotypes such as depression at individual symptom level rather than assessing only a summed score (Fried & Nesse, 2015). It is thought that assessing specific patterns of individual symptoms as well as their potential causal associations will allow for a better understanding of the substantial variations in symptoms across individuals that has led to the status of depression as a diagnosable syndrome being called into question. Such an approach could also allow for a better understanding of how potential intermediate phenotypes such as cognitive biases impact on specific symptoms and whether such associations are confined to specific types or clusters of symptoms and how this may feed into the overall phenotype of depression.

Lastly, future research should also consider significant increases in sample size in order to assess the potential differential effects of gender, as this has been demonstrated in previous research. For example, a previous meta-analysis examining the effectiveness of interpretation bias modification at increasing positive interpretation and mood has demonstrated that women benefit significantly more than men regarding improvements in both bias and mood (Menne-Lothmann et al., 2014). Furthermore, a separate study has also shown significant differences between males and females in terms of BDNF rs6265 and the development of memory bias, with an interaction between stressful life events and rs6265 genotypes being associated with a memory bias in men but not women (van Oostrom et al., 2012). This is particularly interesting as study two (chapter

three) also highlighted the same variant (rs6265) as the most consistently significant finding, moderating the effects of both positive and negative life events on memory bias. Further assessment of genetic effects in the development of multiple cognitive biases across genders will likely provide valuable insight into potential mechanisms that may be driving such differences. This could also inform novel gender specific cognitive bias modification techniques as well as the identification of those most likely to benefit based on genotypes associated to gender specific outcomes, potentially increasing the overall efficacy of existing, and new prevention and treatment approaches.

In addition to the assessment of gender differences, increased statistical power through larger sample size, would also allow for a more in-depth assessment of the potential causal impact of cognitive biases on depression and anxiety. For example, whilst not a desired aim of study three (chapter five), limited power, and the subsequent drop off of nearly a fifth of the participants, would have rendered the sample underpowered to assess causality in more depth using approaches such as structural equation modelling. It is thought that such modelling, using data from multiple waves of data collection in large enough samples, and with the inclusion of life events, will provide much more conclusive results regarding the causal effects of cognitive biases.

6.6. Conclusion

To conclude, the current thesis has, for the first time, demonstrated the effects of cognitive biases, and specifically interpretation bias, as being a significant factor impacting on PA throughout the course of daily life and in reaction to specific environmental contexts. Furthermore, it has also been shown that such cognitive biases develop as a result of both positive and negative life events, variations in specific genetic variants implicated in previous GxE research of affective disorders, as well as the interplay between these factors. Lastly, research presented here has also demonstrated a shared genetic architecture between affective disorders and positive components of cognitive biases, highlighting elements of such biases as important intermediate phenotypes. These findings have important implications regarding treatment and intervention targets and strategies, as well as the development of novel strategies that could be aimed at preventing or treating both affective states and disorders.

However, there is still much work to be done before a definitive conclusion regarding the causal impact of cognitive biases on affective disorders can be made. Despite this, the current

thesis represents a solid first step and provides a unique platform for further research to continue such assessments, replicate, and extend on the novel findings demonstrated here. Furthermore, despite providing partial support for the CogBIAS hypothesis, it has also become evident that such relationships, proposed in the original model, have greater complexity than originally conceptualised. It is important that the amendments highlighted and discussed above are incorporated, as this will likely increase the reliability of future iterations of the CogBIAS hypothesis. Following such amendments, there is also the need for further tests of the CogBIAS hypothesis that incorporate the suggested future directions made above and build on the current findings. This will likely provide important knowledge regarding the complex associations between genes, environments, cognitive biases and psychopathology, potentially having further implications for the development of intervention and treatment strategies.

Appendix

i. Descriptive statistics for each of the CASE items.

Table i.i. Endorsed CASE items and their frequency of being rated as either positive or negative across each of the three time points

	Wave 1			Wave 2			Wave 3		
	Endorsed	Rated negative	Rated positive	Endorsed	Rated negative	Rated positive	Endorsed	Rated negative	Rated positive
CASE item	n	n (%)	n (%)	n	n (%)	n (%)	n	n (%)	n (%)
We moved house	108	9 (8.3)	99 (91.6)	81	7 (8.6)	74 (91.3)	64	8 (12.5)	56 (87.5)
I (or my team) won a prize, award or contest	359	1 (0.2)	358 (99.7)	303	2 (0.6)	301 (99.3)	252	0 (0)	252 (100)
My parent(s) stayed away from home overnight	287	115 (40)	172 (59.9)	295	107 (36.2)	188 (63.7)	263	81 (30.8)	182 (69.2)
I got a new boyfriend or girlfriend	113	6 (5.3)	107 (94.6)	119	10 (8.4)	109 (91.6)	102	9 (8.8)	93 (91.1)
My parent(s) started a new job	177	13 (7.3)	164 (92.6)	147	18 (12.2)	129 (87.7)	128	13 (10.1)	115 (89.8)
Someone special to me moved away (who is not in your family)	118	116 (98.3)	2 (1.6)	91	83 (91.2)	8 (8.7)	49	47 (95.9)	2 (4)
Someone in my family was really sick or injured	273	268 (98.1)	5 (1.8)	226	221 (97.7)	5 (2.2)	193	190 (98.4)	3 (1.5)
My parent(s) had a baby/found out they are going to have a baby	45	6 (13.3)	39 (86.6)	30	3 (10)	27 (90)	18	2 (11.1)	16 (88.8)
My parent(s) had to see my school principle	81	48 (59.2)	33 (40.7)	57	37 (64.9)	20 (35)	44	28 (63.6)	16 (36.3)

I stayed away from home overnight	408	33 (8)	375 (91.9)	379	22 (5.8)	357 (94.2)	357	33 (9.2)	324 (90.7)
Someone came to live with our family	110	17 (15.4)	93 (84.5)	91	22 (24.1)	69 (75.8)	88	17 (19.3)	71 (80.6)
I was teased or bullied	154	146 (94.8)	8 (5.1)	127	118 (92.9)	9 (7)	99	95 (95.9)	4 (4)
My pet died, got sick, lost or injured	170	165 (97)	5 (2.9)	146	139 (95.2)	7 (4.7)	105	102 (97.1)	3 (2.8)
I had a big argument with someone in our family	199	191 (95.9)	8 (4)	196	177 (90.3)	19 (9.6)	189	176 (93.1)	13 (6.8)
I was really sick or injured	146	137 (93.8)	9 (6.1)	102	95 (93.1)	7 (6.8)	90	86 (95.5)	4 (4.4)
My parent(s) split up	34	30 (88.2)	4 (11.7)	26	19 (73)	7 (26.9)	21	18 (85.7)	3 (14.2)
I did well in an important test or exam	388	4 (1)	384 (98.9)	351	4 (1.1)	347 (98.8)	315	3 (0.9)	312 (99)
My parent(s) lost their job	27	24 (88.8)	3 (11.1)	30	24 (80)	6 (20)	25	24 (96)	1 (4)
I broke up with my boyfriend or girlfriend	99	66 (66.6)	33 (33.3)	92	69 (75)	23 (25)	85	61 (71.7)	24 (28.2)
I had a big argument with someone special to me (not in family)	179	173 (96.6)	6 (3.3)	155	138 (89)	17 (10.9)	149	138 (92.6)	11 (7.3)
I made a new special friend	290	5 (1.7)	285 (98.2)	237	6 (2.5)	231 (97.4)	160	4 (2.5)	156 (97.5)
I saw something bad happen	114	110 (96.4)	4 (3.5)	81	75 (92.5)	6 (7.4)	73	68 (93.1)	5 (6.8)
I changed schools	194	16 (8.2)	178 (91.7)	37	11 (29.7)	26 (70.2)	24	4 (16.6)	20 (83.3)
Someone in the family died	142	139 (97.8)	3 (2.1)	121	114 (94.2)	7 (5.7)	106	104 (98.1)	2 (1.8)
People in the family had a big fight or argument (not including me)	161	155 (96.2)	6 (3.7)	175	167 (95.4)	8 (4.5)	151	146 (96.6)	5 (3.3)
My mum got married, engaged or began seeing someone else	37	17 (45.9)	20 (54)	30	7 (23.3)	23 (76.6)	24	8 (33.3)	16 (66.6)

Someone broke into my house	23	22 (95.6)	1 (4.3)	21	18 (85.7)	3 (14.2)	15	14 (93.3)	1 (6.6)
Someone in my family left home	40	32 (80)	8 (20)	47	34 (72.3)	13 (27.6)	36	21 (58.3)	15 (41.6)
I was in a fight (not with people in my family)	103	88 (85.4)	15 (14.5)	87	69 (79.3)	18 (20.6)	61	47 (77)	14 (22.9)
I did badly in an important test or exam	241	237 (98.3)	4 (1.6)	253	246 (97.2)	7 (2.7)	212	210 (99)	2 (0.9)
Someone special to me died (who was not in your family)	64	63 (98.4)	1 (1.5)	46	44 (95.6)	2 (4.3)	37	36 (97.3)	1 (2.7)
I was chosen to be a class monitor, prefect or school captain	160	3 (1.8)	157 (98.1)	100	5 (5)	95 (95)	72	2 (2.7)	70 (97.2)
I was seriously told of or punished by a teacher	117	101 (86.3)	16 (13.6)	104	96 (92.3)	8 (7.6)	86	78 (90.7)	8 (9.3)
I took up a new hobby/sport/activity	322	4 (1.2)	318 (98.7)	236	4 (1.6)	232 (98.3)	183	0 (0)	183 (100)
I found out I had to repeat a grade in school	10	7 (70)	3 (30)	7	4 (57.1)	3 (42.8)	3	1 (33.3)	2 (66.6)
Someone special to me was really sick or injured (not in family)	90	87 (96.6)	3 (3.3)	69	65 (94.2)	4 (5.8)	38	36 (94.7)	2 (5.2)
My dad got married, engaged or began seeing someone else	35	14 (40)	21 (60)	33	19 (57.5)	14 (42.4)	21	10 (47.6)	11 (52.3)
I went on a special holiday	376	6 (1.6)	370 (98.4)	334	6 (1.8)	328 (98.2)	308	4 (1.3)	304 (98.7)

Note: Displayed The number of individuals endorsing each item of the CASE at each of the three timepoints. Also displayed are the percentages of individuals reporting an endorsed item as positive or negative as dichotomized from the original three positive and three negative options from the 6-point Likert scale. Percentages highlighted in red represent all life events interpreted as negative by over 90% of individuals that had taken part. Percentages highlighted in green represent all life events interpreted as positive by over 90% of individuals. Percentages highlighted in yellow represent ambiguous life events interpreted as either positive or negative as defined by percentages of between 30-70%.

ii. Results of a logistic regression examining the effect of cognitive biases on the subjective rating of items in the CASE questionnaire across all three timepoints.

Table ii.i. The effect of cognitive biases in memory, social and non-social interpretation bias on subjective ratings of each individual CASE item across all timepoints

CASE item	Memory Bias			Social Interpretation Bias			Non-social Interpretation Bias		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
We moved house	1.08	0.43-2.72	0.865	0.88	0.59-1.32	0.529	0.69	0.42-1.12	0.137
I (or my team) won a prize, award or contest	0.65	0.05-8.41	0.745	0.72	0.52-1.00	**0.047***	2.24	0.53-9.42	0.273
My parent(s) stayed away from home overnight	1.86	1.32-2.64	**4.6×10^{-4} ***	1.26	1.10-1.44	**0.001***	1.38	1.17-1.62	**9.18×10^{-5}***
I got a new boyfriend or girlfriend	1.69	0.60-4.73	0.322	1.76	1.27-2.46	**0.001***	1.46	1.04-2.03	0.028
My parent(s) started a new job	4.09	2.12-7.90	**2.77×10^{-5}***	1.83	1.41-2.38	**6.30×10^{-6}***	1.43	1.01-2.04	0.045
Someone special to me moved away (who is not in your family)	0.91	0.30-2.77	0.870	1.44	0.87-2.41	0.160	0.79	0.38-1.64	0.519
Someone in my family was really sick or injured	1.99	0.33-11.87	0.451	1.38	0.82-2.32	0.225	0.82	0.46-1.46	0.497
My parent(s) had a baby/found out they are going to have a baby	0.44	0.08-2.33	0.332	1.34	0.89-2.02	0.162	0.91	0.48-1.72	0.762
My parent(s) had to see my school principle	1.31	0.59-2.93	0.504	1.46	1.08-1.99	0.014	1.49	1.06-2.09	**0.022***
I stayed away from home overnight	4.08	2.34-7.11	**7.41×10^{-7}***	1.52	1.23-1.87	**7.42×10^{-5}***	1.72	1.35-2.20	**1.12×10^{-5}***
Someone came to live with our family	2.57	1.22-5.39	**0.013***	1.2	0.92-1.57	0.175	1.33	0.95-1.86	0.099

I was teased or bullied	0.92	0.43-2.00	0.836	1.36	0.88-2.12	0.168	0.93	0.62-1.40	0.728
My pet died, got sick, lost or injured	0.49	0.12-1.96	0.315	1.07	0.61-1.87	0.812	0.55	0.34-0.90	0.017
I had a big argument with someone in our family	1.56	0.69-3.52	0.281	1.45	1.07-1.97	**0.017***	0.84	0.58-1.22	0.363
I was really sick or injured	1.78	0.46-6.92	0.403	1.35	0.81-2.26	0.249	1.21	0.72-2.03	0.464
My parent(s) split up	0.34	0.12-0.98	**0.047***	0.88	0.54-1.41	0.585	0.55	0.29-1.07	0.077
I did well in an important test or exam	2.07	0.57-7.56	0.270	0.91	0.50-1.66	0.764	1.73	1.00-2.99	0.051
My parent(s) lost their job	3.17	0.43-23.54	0.258	0.94	0.53-1.69	0.846	1	0.41-2.44	0.998
I broke up with my boyfriend or girlfriend	1.23	0.68-2.21	0.495	0.98	0.78-1.24	0.880	0.94	0.72-1.22	0.626
I had a big argument with someone special to me (who is not in your family)	1.34	0.52-3.42	0.543	1.47	1.09-2.00	**0.013***	1.11	0.82-1.50	0.505
I made a new special friend	6.63	2.06-21.35	**0.002***	1.81	1.03-3.18	**0.041***	2.24	1.28-3.91	**0.005***
I saw something bad happen	0.84	0.20-3.61	0.815	1.52	0.84-2.76	0.167	0.72	0.34-1.51	0.382
I changed schools	2.86	1.16-7.08	**0.023***	1.1	0.78-1.55	0.586	1.52	1.03-2.23	**0.034***
Someone in the family died	0.4	0.13-1.21	0.105	1.15	0.64-2.05	0.644	0.68	0.39-1.20	0.186
People in the family had a big fight or argument (not including me)	0.67	0.23-2.00	0.476	1.06	0.69-1.63	0.798	0.64	0.44-0.92	**0.017***
My mum got married, engaged or began seeing someone else	0.73	0.28-1.89	0.512	0.96	0.68-1.35	0.813	0.91	0.56-1.48	0.703

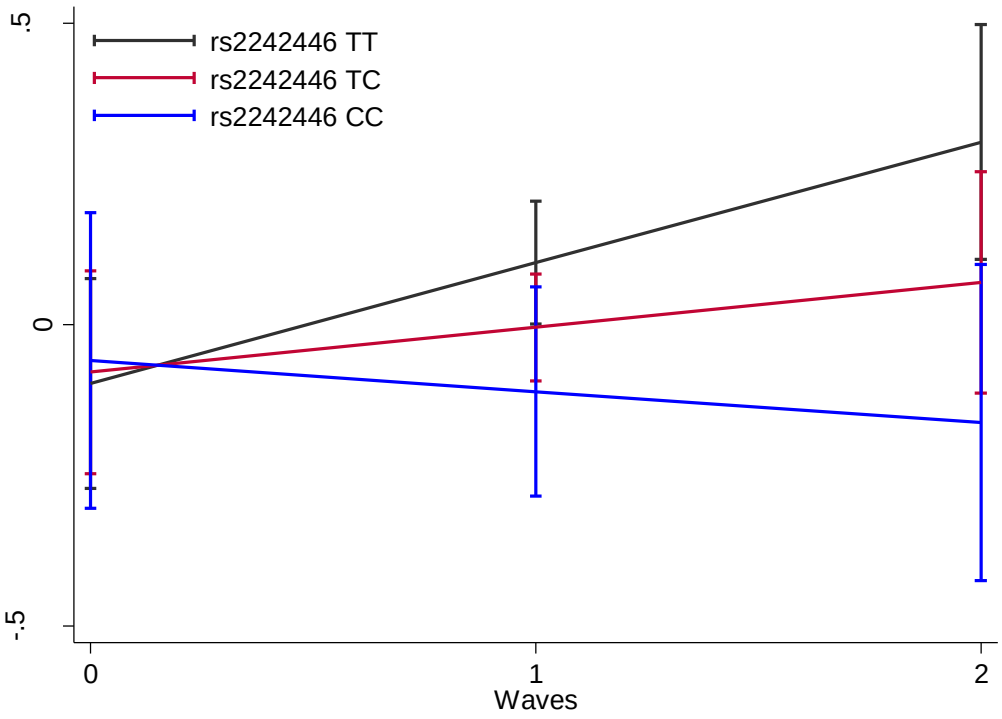
Someone broke into my house	0.28	0.06-1.42	0.124	1.57	0.92-2.66	0.097	0.85	0.46-1.57	0.604
Someone in my family left home	1.54	0.68-3.48	0.295	1.38	1.04-1.83	**0.028***	1.29	0.86-1.93	0.217
I was in a fight (not with people in my family)	1.83	0.84-3.99	0.130	1.66	1.25-2.21	**4.50×10^{-4}***	1.54	1.09-2.17	**0.014***
I did badly in an important test or exam	1.01	0.28-3.70	0.986	1.49	0.80-2.77	0.208	0.55	0.35-0.87	**0.010***
Someone special to me died (who was not in your family)	0.18	0.01-3.16	0.240	0.93	0.37-2.31	0.868	0.4	0.16-0.95	**0.039***
I was chosen to be a class monitor, prefect or school captain	1.07	0.26-4.40	0.924	0.89	0.46-1.73	0.736	2.02	0.85-4.82	0.113
I was seriously told of or punished by a teacher	1.78	0.54-5.87	0.345	1.29	0.86-1.95	0.216	0.79	0.57-1.07	0.131
I took up a new hobby/sport/activity	1.61	0.26-10.01	0.610	1.38	0.70-2.74	0.352	1.03	0.47-2.26	0.941
I found out I had to repeat a grade in school	0.83	0.11-6.43	0.856	1.55	0.67-3.60	0.308	0.73	0.25-2.08	0.554
Someone special to me was really sick or injured (who is not in your family)	0.35	0.09-1.36	0.129	1.03	0.56-1.90	0.928	1.01	0.40-2.54	0.992
My dad got married, engaged or began seeing someone else	2.14	0.90-5.08	0.083	1.16	0.84-1.60	0.377	1.04	0.63-1.70	0.891
I went on a special holiday	2.54	1.02-6.36	**0.046***	1.22	0.74-2.01	0.430	1.45	0.86-2.45	0.168

Note: Results from the three cognitive biases (memory bias, social interpretation bias, non-social interpretation bias) are displayed. Significant results indicate that the bias is associated with the way in which the item is interpreted and rated, therefore confounding the results.

iii. Candidate variant-by-time simple slopes and margin plots.

Simple slope analysis regarding the interaction between timepoint and rs2242446 in SLC6A2 on memory bias revealed a non-significant positive association of time in TT and CT genotypes (β=0.17, 95%CI=-0.04-0.37, *p*=0.108 and β=0.17, 95%CI=-0.08-0.43, *p*=0.183 respectively) and a non-significant negative association of time in CC genotypes (β=-0.30, 95%CI=-0.69-0.09, *p*=0.128). That is, memory bias showed a small increase for those with TT and CT genotypes and a small decrease for those with CC genotypes over time (see **Figure iii.i**).

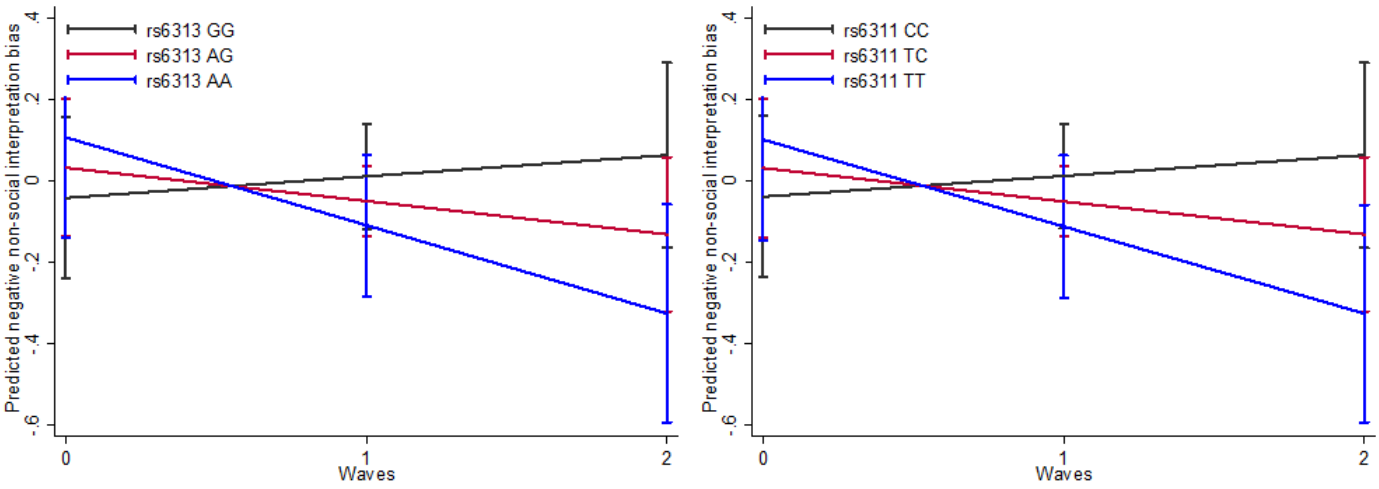
Figure iii.i. Margin plot displaying the predicted memory bias for each wave for those with TT, CT or CC genotypes at rs2242446 in *SLC6A2*.



Simple slope analyses regarding the interaction between timepoint and rs6313 suggested that in individuals with the AA genotype at rs6313, wave was negatively associated with negative non-social interpretation (β=-0.44, 95%CI=-0.829--0.052, *p*=0.026) however, wave was not significant for those with other genotypes at this locus (AG: β=-0.13, 95%CI=-0.35-0.09, *p*=0.252; GG: β=0.21, 95%CI=-0.06-0.48, *p*=0.125). These associations are further illustrated in **Figure**

iii.ii below illustrating that those with the AA genotype at rs6313 experienced a large decrease in negative non-social interpretation bias, while those with the AG or GG genotypes experienced a non-significant decrease and a non-significant increase in negative non-social interpretation bias, respectively. The pattern of results was similar for rs6311 which is in high LD with rs6313 also shown in the **Figure iii.ii** below. Specifically, the association of wave across these genotypes were: β=-0.44, 95%CI=-0.83--0.05, *p*=0.026; β=-0.12, 95%CI=-0.34-0.10, *p*=0.277; β=0.20, 95%CI=-0.07-0.46, *p*=0.149 in those with TT, TC and CC genotypes respectively.

Figure iii.ii. Margin plot displaying the identical effects of both the rs6313 in HTR2A (left), and the rs6311 in HTR2A (right) genotype by time interaction over three time points.

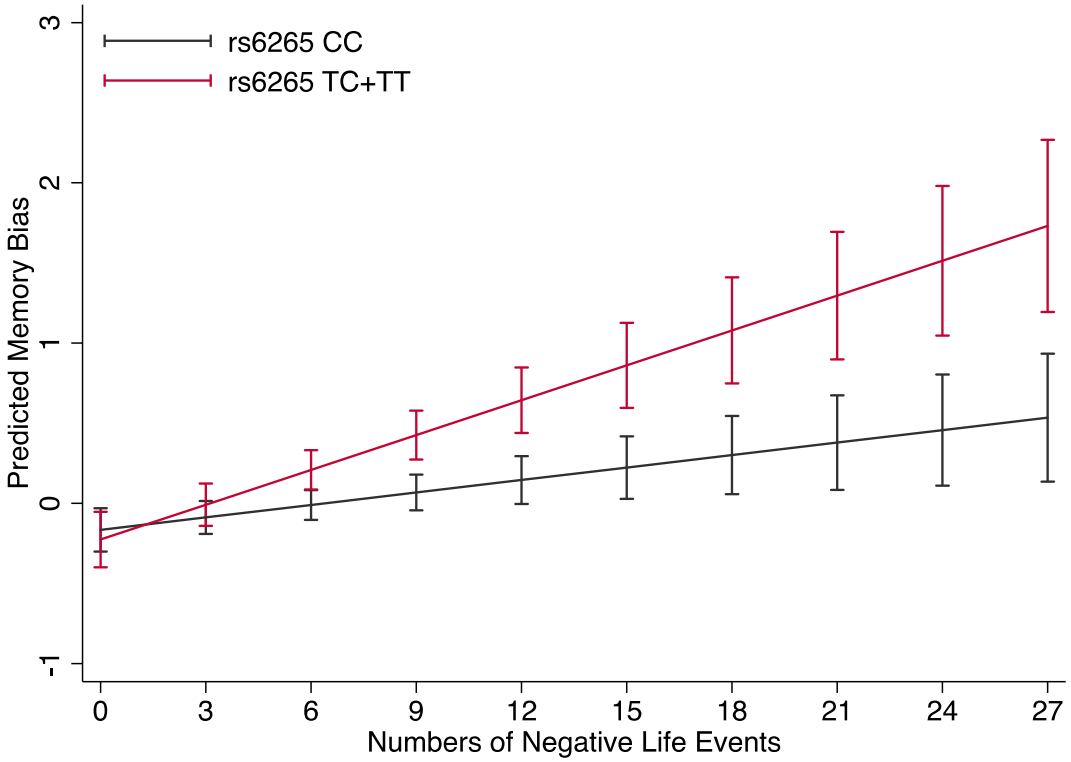


Note: The identical results are due to these variants existing very close together on the same gene thereby having near identical effects.

iv. Candidate variant-by-negative life event simple slopes and margin plots.

Simple slope analyses showed that for those within the TC/TT genotype group at BDNF (rs6265) there was a significant positive relationship between the number of negative life events experienced and memory bias scores (β=0.31, 95%CI=0.21-0.40, p=9.38x10^{-10}). A significant positive association was also observed for the C-allele homozygotes at this locus (β=0.10, 95%CI=0.03-0.17, p=0.005), albeit to a much lesser extent. These findings are further illustrated below in **Figure iv.i** which shows that as the number of negative life events increase, memory bias score become more negative. However, the association regarding negative life events differed according to the genotypic group. Specifically, negative life events had a greater association with T-allele carriers compared to those with the homozygote CC genotype.

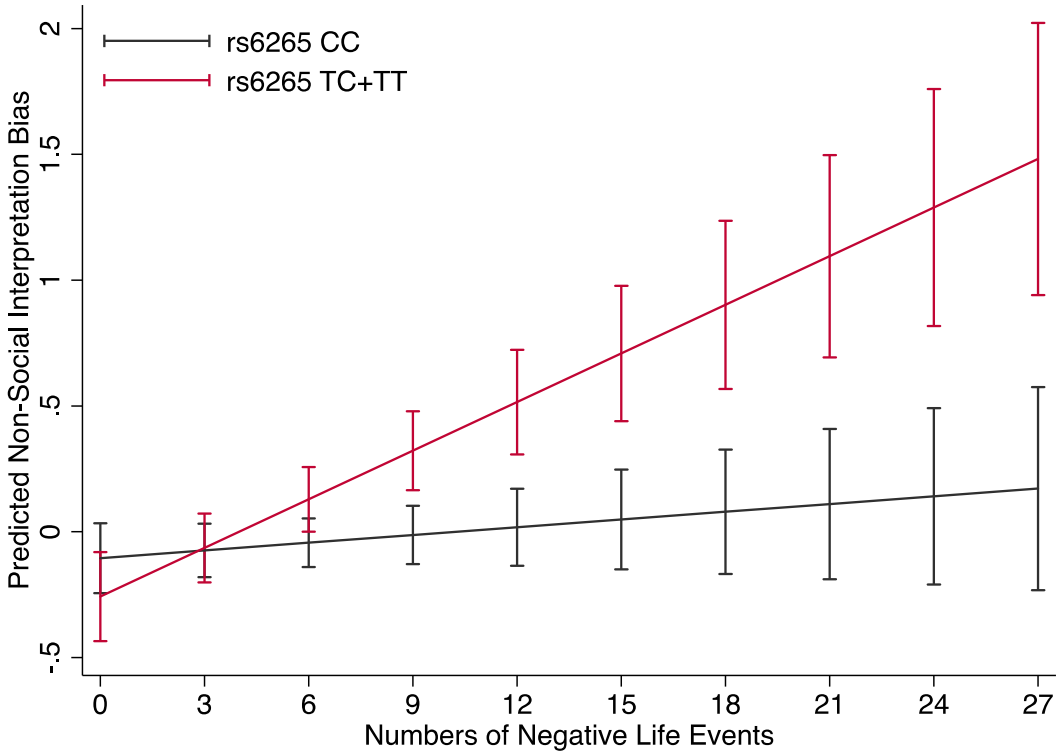
Figure iv.i. Margins plot displaying the predicted effects of negative life events on memory bias by BDNF genotypes.



Note: Two genotypic groups are represented by each of the two lines. The red line represents TC and TT genotypes, and the black line represents a CC genotype. The number of negative life events are shown in integers of three on the X axis.

Simple slope analyses of the interaction between rs6265 and negative life events on non-social interpretation bias revealed similar findings. That is, the association between negative life events and non-social interpretation bias were greater in the T-allele carriers (β=0.25, 95%CI=0.15-0.35, p=7.58x10^{-7}) than those with the CC genotype (β=0.04, 95%CI=-0.03-0.11, p=0.257). These findings are illustrated below in **Figure iv.ii**.

Figure iv.ii. Margins plot displaying the predicted effects of negative life events on non-social interpretation bias by BDNF genotypes.

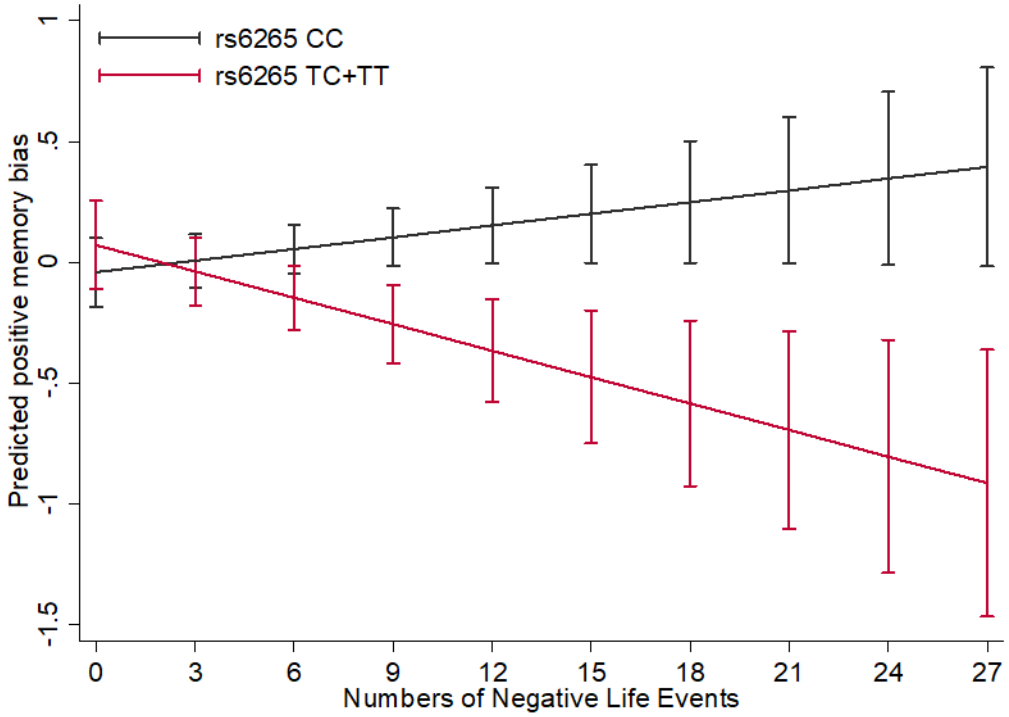


Note: Two genotypic groups are represented by each of the two lines. The red line represents TC and TT genotypes, and the black line represents a CC genotype. The number of negative life events are shown in integers of three on the X axis.

Simple slopes analyses regarding the interaction between BDNF (rs6265) and negative life events on the positive component of memory bias (*positive memory bias*) was consistent with the previous analyses regarding the interaction between BDNF (rs6265) and negative life events on memory bias. That is, negative life events had a greater negative association with the positive component of memory bias (*positive memory bias*) in individuals carrying the T-allele (TC/TT)

(β=-0.15, 95%CI=-0.25--0.06, *p*=0.002), compared to those with the CC genotype at this locus (β=0.07, 95%CI=-0.01-0.14, *p*=0.084). These associations are illustrated in **Figure iv.iii** demonstrating that as the number of negative life events increases, the positive component of memory bias (*positive memory bias*) in the T-allele carriers of rs6265 significantly decreases. However, for the C allele homozygotes there is a non-significant increase in the positive component of memory bias (*positive memory bias*) as numbers of negative life events increase.

Figure iv.iii. Margin plot displaying the predicted effects of negative life events on the positive memory bias component (positive memory bias) by BDNF genotypes.

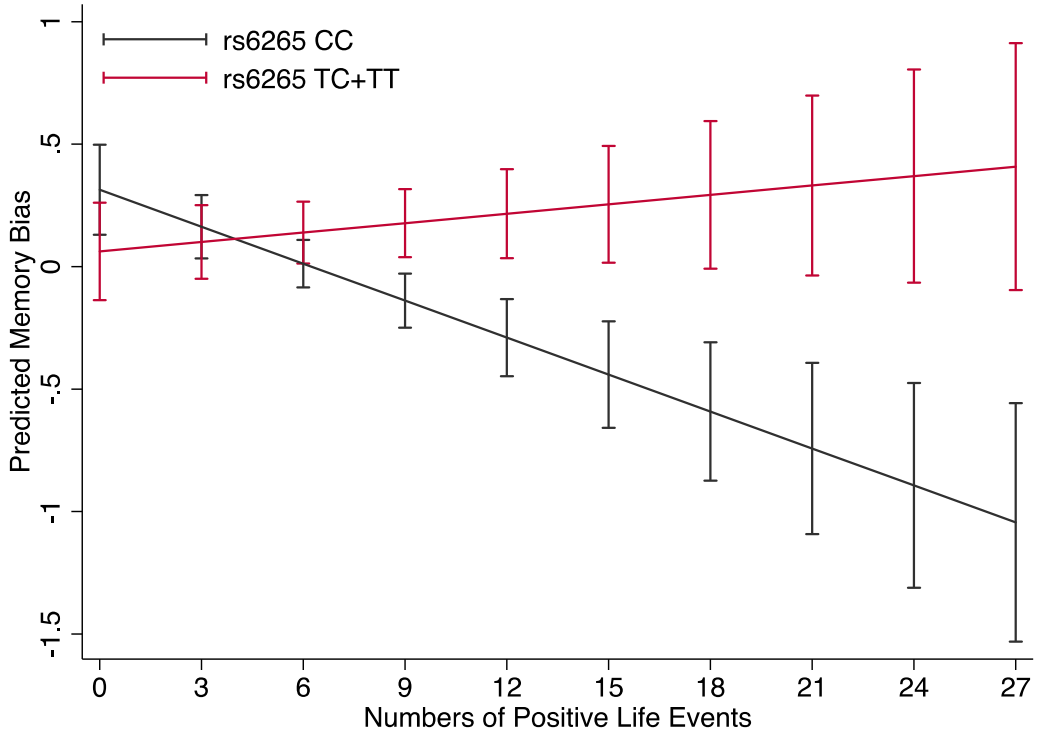


Note: Two genotypic groups are represented by each of the two lines. The red line represents TC and TT genotypes, and the black line represents a CC genotype. The number of negative life events are shown in integers of three on the X axis.

v. Candidate variant-by-positive life event simple slopes and margin plots.

Simple slope analyses demonstrate that positive life events were negatively associated with memory bias in individuals with the CC genotype at rs6265 (β=-0.17, 95%CI=-0.25--0.10, p=5.27x10^{-6}). That is, positive life events resulted in a positive memory bias. However, in individuals carrying the T-allele at the same locus, positive life events did not significantly influence memory bias (β=0.04, 95%CI=-0.04-0.13, p=0.34). These associations are illustrated below in **Figure v.i**.

Figure v.i. Margin plot displaying the predicted effects of positive life events on memory bias by BDNF genotypes.

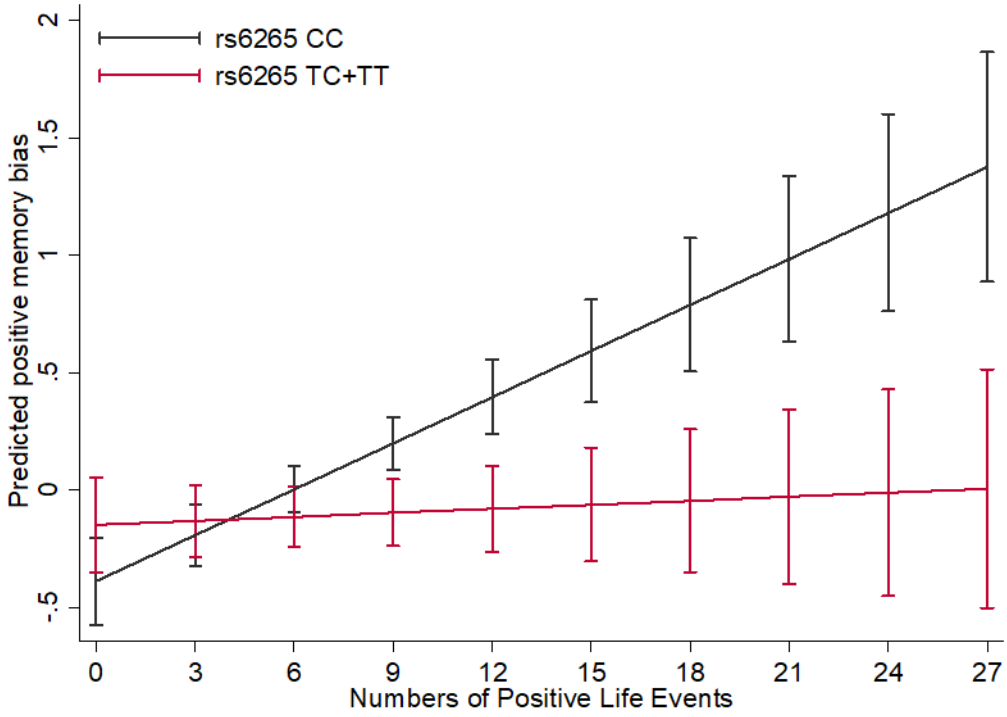


Note: Two genotypic groups are represented by each of the two lines. The red line represents TC and TT genotypes, and the black line represents a CC genotype. The number of negative life events are shown in integers of three on the X axis.

Simple slope analysis examining the interaction between rs6265 and positive life events on the positive component of memory bias (*positive memory bias*) highlighted a significant positive association with CC carriers of rs6265 (β=0.22, 95%CI=0.15-0.30, p=2.28x10^{-8}), with an increase

in positive life events increasing the frequency of positive words endorsed and recalled in the SRET. However, for carriers of the T-allele the effect of positive life events on the positive component of memory bias (*positive memory bias*) was small and non-significant (β=0.02, 95%CI=-0.06-0.09), p=0.693). These effects are illustrated below in **Figure v.ii**.

Figure v.ii. Margin plot displaying the predicted effects of positive life events on the positive memory bias component (positive memory bias) by BDNF genotypes.

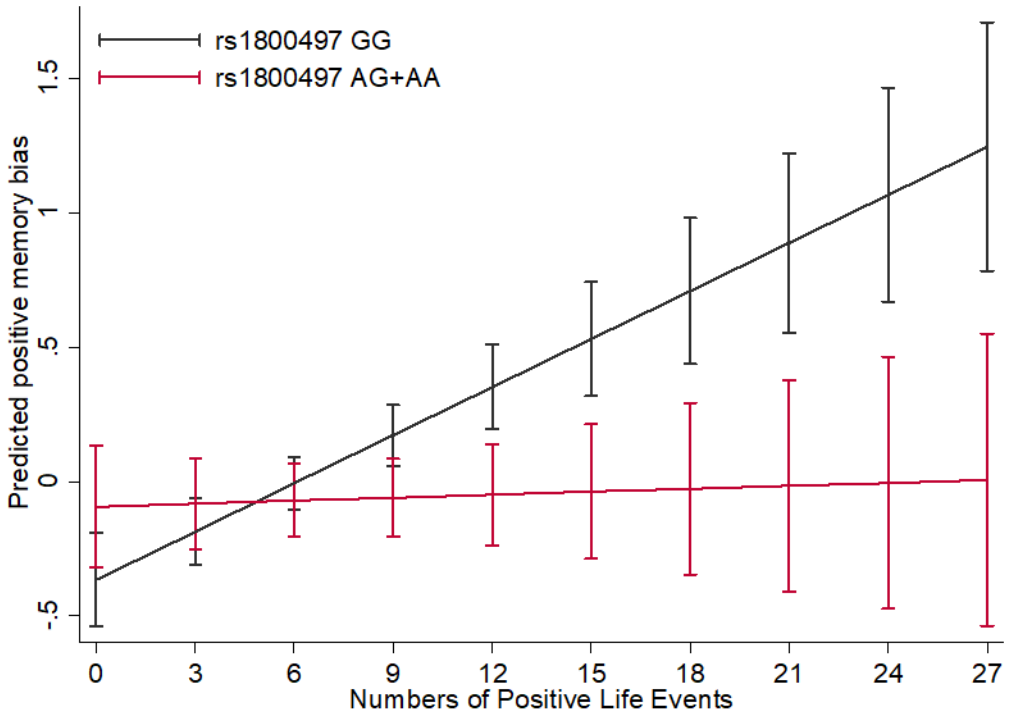


Note: Two genotypic groups are represented by each of the two lines. The red line represents TC and TT genotypes, and the black line represents a CC genotype. The number of negative life events are shown in integers of three on the X axis.

Simple slope analysis of the interaction between rs1800497 and positive life events on the positive component of memory bias (*positive memory bias*) were very similar to those of the same interaction involving rs6265. For those individuals' homozygote for the G-allele there was a significant positive association between positive life events and the positive component of memory bias (*positive memory bias*: β=0.19, 95%CI=0.12-0.26, $p=1.39x10^{-7}$). This effectively resulted in more words positively endorsed and recalled in the SRET task as the number of positive life events increased. However, for the A-allele carriers, the association between positive life events and the

positive component of memory bias (*positive memory bias*) was small and non-significant (AG and AA: β=0.02, 95%CI=-0.07-0.11, *p*=0.677). These effects are illustrated below in **Figure v.iii**.

Figure v.iii. Margin plot displaying the predicted effects of positive life events on the positive memory bias component (positive memory bias) by DRD2 (rs1800497) genotypes.



Note: Two genotypic groups are represented by each of the two lines. The red line represents AG and AA genotypes, and the black line represents a GG genotype. The number of positive life events are shown in integers of three on the X axis.

vi. Principle component analysis and residual PRS distribution.

Ten principal components were identified and selected in order to control for population stratification amongst the sample. The association between the 10 principal components and the cognitive biases, as well as their positive and negative components, were assessed across all waves using a linear mixture model with age and gender as covariates, whilst also controlling for the fixed and random effects of wave. The results are provided in the table below (**Table vi.i**). The association between the same 10 principal components and each threshold of the raw MDD PRS were also assessed across all waves using linear regression. Results are provided in **Table vi.ii**.

Table vi.i. Table displaying the associations between each of the cognitive bias and their corresponding positive and negative components and each of the ten principal components across all three waves.

	Pc1	Pc2	Pc3	Pc4	Pc5	Pc6	Pc7	Pc8	Pc9	Pc10
Memory bias	**0.08***	0.05	0.03	0.01	0.03	0.02	-0.06	-0.06	0.04	0.01
Positive endorsed and recalled	-0.05	**-0.11****	-0.04	0.07	-0.04	0	0.01	**0.09***	-0.03	-0.04
Negative endorsed and recalled	**0.08***	0.02	0.03	0.03	0.03	0	-0.02	0	0.02	0
Social interpretation bias	0.05	0.07	0.01	0	0	0	-0.04	-0.01	-0.01	0
Positive social interpretation	-0.05	-0.05	0.01	-0.01	0	0.01	0.02	0.01	0.03	0
Negative social interpretation	0.03	0.06	0.03	0	0	0	-0.04	-0.01	0.01	0
Non-social interpretation bias	0.04	0.03	0.05	0.05	-0.03	0	**0.08***	**-0.12****	0.02	-0.02
Positive non-social interpretation	**-0.09***	-0.04	-0.05	-0.05	0.04	0	-0.06	**0.1****	0	0.05
Negative non-social interpretation	-0.02	0	0.01	0.03	-0.01	-0.01	0.06	**-0.08***	0.03	0.03

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

Table vi.ii. Table displaying the associations between each of the eight selected MDD PRS *p*-value thresholds (PT) and each of the ten principal components across all three waves.

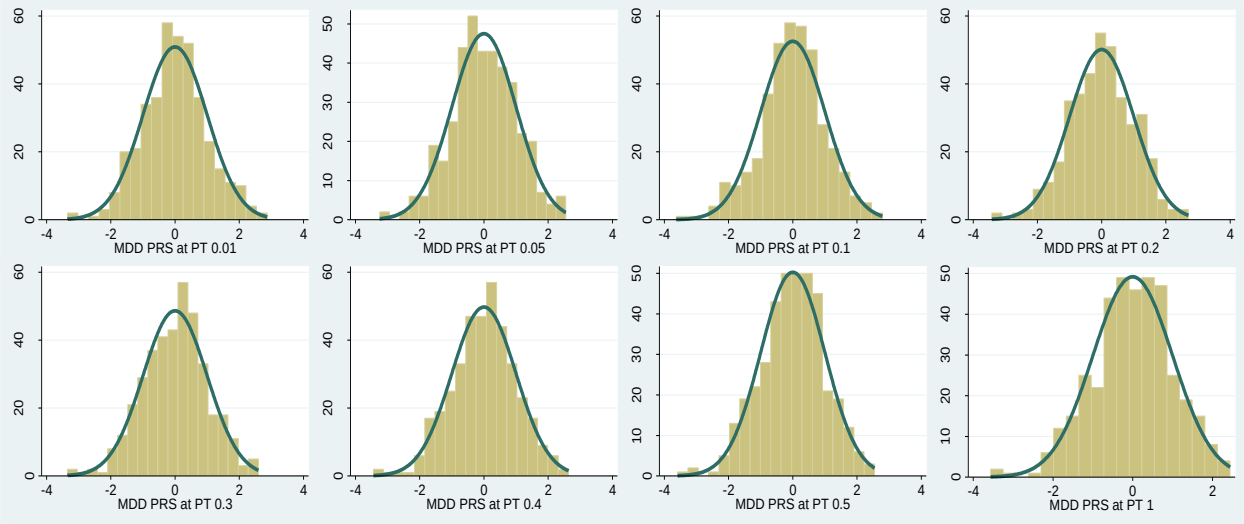
MDD PRS PT	Pc1	Pc2	Pc3	Pc4	Pc5	Pc6	Pc7	Pc8	Pc9	Pc10
PT 0.01	**-1.08****	0.72	-0.35	0.07	0.07	-0.02	-0.1	-0.12	-0.04	-0.03
PT 0.05	**-1.06****	0.67	**-1.11***	0.13	**0.17*****	0.04	-0.06	-0.08	-0.02	-0.02
PT 0.1	**-1.13****	1.23	-0.58	0.08	**0.14****	0.02	-0.1	**-0.19****	-0.01	-0.03
PT 0.2	**-1.11****	1.23	-0.42	0.09	**0.12***	0	-0.11	**-0.18****	-0.06	-0.01
PT 0.3	**-1.17*****	1.23	-0.68	0.08	**0.1***	0.01	-0.1	**-0.2****	-0.02	-0.02
PT 0.4	**-1.16*****	1.17	-0.66	0.08	**0.1***	0.02	-0.1	**-0.2****	-0.03	-0.01
PT 0.5	**-1.18*****	1.18	-0.67	0.09	0.1	0.02	-0.1	**-0.18****	-0.04	-0.02
PT 1	**-1.16*****	1.1	-0.65	0.08	0.1	0.01	-0.09	**-0.18****	-0.04	-0.01

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

As can be seen from the results above (**Table vi.i**), only principal components one, two, seven and eight had significant association with one of more of the cognitive biases, or their positive and negative components. Similarly, results regarding the associations between the principal components and the MDD PRS thresholds (**Table vi.ii**), highlighted principal components one, three, five and eight as significantly associated with one or more of the MDD PRS thresholds. However, despite some principal components falling short of having a significant effect on either the cognitive biases, their positive and negative components, or the MDD PRS thresholds, there were effects that likely contribute. These non-significant effects likely have a cumulative effect that should be taken into account. Therefore, in order to air on the side of caution, control for population stratification within the sample, and avoid type 1 error, all ten principal components were partialled out to create a residual MDD PRS score.

Following this, the distribution of the new residual MDD PRS across the CogBIAS-L-S sample (Europeans only) was assessed at each of the MDD PRS p-value thresholds. Histograms displaying the results of these analyses can be found in **Figure vi.i**.

Figure vi.i. Histograms displaying the distributions of the MDD PRS for all individuals within the CogBIAS sample. The distribution was assessed at all eight p-value thresholds (PT).



In both sets of the analyses the distribution of the MDD PRS were within acceptable range at all PRS thresholds. The distribution skewness across the CogBIAS-L-S sample ranged from 0.034 at p-value threshold 0.01 to -0.27 at p-value threshold 1. Kurtosis of these distributions ranged from 3.03 at p-value threshold 0.05 to 3.37 at p-value threshold 0.1.

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