Genetics of Environmental Sensitivity and its Moderating Effects on Mental Health Outcomes

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Submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy

Queen Mary University of London

Statement of originality

I, Elham Assary, 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.

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Details of collaboration and publications:

The following publications resulted from work presented in this thesis. All original analyses in this thesis were conducted by the author (except for test-re-rest analysis in Chapter 2 by Kate Lester), with the final version having undergone peer review process and incorporates feedback and contribution from co-authors. None of the data used in the current study were collected by myself.

Chapter 1:

Assary, E., & Pluess, M. (2017). Differential Susceptibility in Minority Children: Individual Differences in Environmental Sensitivity *Handbook on Positive Development of Minority Children and Youth* (pp. 139-152): Springer.

Assary, E., Vincent, J. P., Keers, R., & Pluess, M. (2017). *Gene-environment interaction and psychiatric disorders: Review and future directions.* Paper presented at the Seminars in cell & developmental biology.

Assary, E., Vincent, J. P., Machlitt-Northen, S., Keers, R., & Pluess, M. (In press). The Role of Gene-Environment Interaction in Mental Health and Susceptibility to the Development of Psychiatric Disorders. In R. Teperino (Ed.), *Beyond our Genes: Pathophysiology of Gene and Environment Interaction and Epigenetic Inheritance*: Springer-Nature.

Chapter 2:

Pluess, M., **Assary, E**., Lionetti, F., Lester, K. J., Krapohl, E., Aron, E. N., & Aron, A. (2018). Environmental sensitivity in children: Development of the Highly Sensitive Child Scale and identification of sensitivity groups. *Dev Psychol, 54*(1), 51-70. doi:10.1037/dev0000406

Chapter 3:

Assary, E., Zavos, H. M., keers, R., Krapohl, E., & Pluess, M. (Submitted). Heritability of Environmental Sensitivity and its Overlap with the Big Five Personality Traits. *Psychological Science*.

Chapter 4 & 5:

Assary, E., Keers, R., Fox, E., Krapohl, E., & Pluess, M. (In preparation). Polygenic score of environmental senstivity moderates the effects of psychosocial environment on psychological distress across life-span.

Acknowledgements

This thesis was made possible by the support that I received from a number of people. Firstly, I would like to express my gratitude to Prof. Michael Pluess, my primary supervisor, for all the assistance, guidance and opportunities he provided me with. I am honoured to have been his first PhD student. I would also like to thank Dr Robert Keers, for going above and beyond his role as my second supervisor, guiding me through the labyrinth of analyses for this thesis. I am especially grateful to Rob, for indulging me with his time to discuss at length my ideas and encouraging an atmosphere of intellectual debate.

I would like to thank Prof Robert Plomin, for granting me access to TEDS data. I am forever grateful to Prof Elaine Fox and Prof Luc Goossens for granting me access to the CogBIAS and STRATEGIES data, enabling me to broaden the scope of this thesis. I would also like to acknowledge the funding I received from Queen Mary University of London, which enabled me to undertake PhD studies in the first place.

Many thanks to all my friends and colleagues at Queen Mary, for lending an ear and sharing their teas and chocolate. I would like to especially thank Kirsty, Social Joe, Bird Joe, Miriam, and Hadi, for making my PhD years fun and enjoyable. Jamboree and Ariana nights will be fondly remembered.

Finally, a great big thanks to my family, for always being a safe haven when I needed refuge, good food and comfort, and for reminding me there is more to life than my PhD. Thank you to Matt for being so wonderful, encouraging, positive, and pragmatic in my darkest hours. Thank you to Eskandar for keeping me company during my writing up; so gentle and timely.

Abstract

According to differential susceptibility theories, individuals vary in the extent to which they are impacted by the quality of their environment, with some individuals identified as generally more sensitive than others making them more susceptible to develop psychopathology in adverse contexts but also more likely to benefit from positive environmental contexts such as psychological interventions. Such individual differences in *environmental sensitivity* are hypothesised to have a genetic basis.

This thesis had three main objectives: first, to examine the heritability of environmental sensitivity; second, to identify the molecular genetic variants associated with environmental sensitivity; third, to examine the moderating effects of genetic sensitivity on the impact of negative and positive environmental contexts on mental health.

First a new measure of environmental sensitivity was developed for use with children. Applying this measure, the heritability of environmental sensitivity was estimated via twin modelling and its molecular genetic basis was explored using candidate genes, genome-wide data, gene-based analyses and polygenic scoring. Longitudinal mixed effect regression models were used to examine polygenic score-by-environment interactions involved in predicting psychopathology and treatment response. The samples for all studies comprised of children and adolescents (N= 1,000-2,800).

The results indicated that environmental sensitivity is heritable (47%, CI = 30-53) and genetically correlated with neuroticism, extraversion, depression and anxiety. Candidate gene and GWAS failed to identify molecular genetic factors that were significantly associated with sensitivity, but polygenic scores of personality, depression and wellbeing predicted variations in sensitivity (~ 3%). Genetic sensitivity was found to moderate the outcomes of environmental exposures, with more sensitive children at higher risk of psychological distress in response to poor quality childhood psychosocial environment, but lower risk of distress later in life. High genetic sensitivity was associated with better response to more individualised type of treatment.

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Chapter 1
General introduction to the concept of environmental sensitivity and related research

1.1 Individual differences in response to environmental influences

Individuals differ in their responses to both adverse as well as enriching environments. This heterogeneity in the psychological and physiological responses to environmental factors has been well documented in psychological and psychiatric research (Rutter, 1985). For example, although maltreatment is an established risk factor for depression in adulthood, not all those exposed to it develop the disorder (Cicchetti, 2013; Collishaw et al., 2007). Individual differences in psychopathology in the context of adverse environmental influences has been commonly studied under a person-by-environment interaction model, in which inherent individual characteristics are thought to moderate the impact of a negative environmental influence. The most widely embraced model of such person-environment interaction is the diathesis-stress model (Monroe & Simons, 1991). According to the diathesis-stress model, some individuals, as a function of inherent characteristics (e.g. genes, temperament, personality, physiology) are more vulnerable to the negative impact of adverse influences. Individuals who carry such vulnerability characteristics are thus more likely to succumb to the adverse effects of environmental stressors such as childhood traumas, and, consequently, develop psychopathology. In the absence of such vulnerabilities, however, adverse environmental influences, in and by themselves, my not have the same negative effects. Furthermore, the vulnerability itself may not be detrimental to the individual in the absence of adversity. Hence, the risk for the development of psychopathology is understood to differ as a function of the interaction between the vulnerability and environmental adversity.

This person–by-environment interaction perspective has been influential in the field of individual differences, not only for psychiatric disorders but also in research on resilience (Cicchetti & Toth, 2016; Rutter, 2012). According to this view, individuals who do not follow the expected trajectory from exposure to adversity to disorder are deemed resilient – due either to the absence of the inherent characteristics that make other individuals vulnerable to the effects of adverse exposures, or to the presence of other characteristics that protect them against those effects.

The diathesis-stress model has been important in emphasising the *interaction* between adversity and individual vulnerability/resilience in the risk of developing psychopathology. However, it does not readily explain individual variations in prosperity/flourishing in response to positive/health-promoting aspects of the environment. Apart from a biased focus on risk, adversity and psychopathology, the

main limitation of the diathesis-stress model lies in its apparent lack of consideration of evolutionary-developmental processes. Specifically, with regards to natural selection, what would be the advantage of maintaining traits and their underlying genes/biological processes that infer only vulnerability to environmental stressors?

Over the last two decades, three related but different theoretical frameworks have been developed that emphasize individual differences in *general sensitivity* to (both positive and negative) environmental influences. These evolutionary-inspired developmental models consider both potential disadvantages as well as advantages in relation to sensitivity to environmental influences. These three frameworks include *biological sensitivity to context* (Boyce & Ellis, 2005; Ellis, Essex, & Boyce, 2005), *sensory-processing sensitivity* (Aron & Aron, 1997) and the *differential susceptibility hypothesis* (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009). All three frameworks build on the underlying dynamic of the diathesis-stress model, whereby variability in developmental/mental health outcomes is considered the result of the interaction between environmental factors and individual characteristics. However, rather than considering these individual characteristics as *vulnerability* factors that increase susceptibility to the detrimental effects of adverse environments, they consider these factors as *sensitivity* markers that predispose the individual to be more responsive to both negative *and* positive environmental influences. From this perspective, heightened sensitivity to environmental influences infers advantages when these influences are positive in valence, but disadvantage when they include stressors/risk.

It must be emphasised that the diathesis-stress model and the more recent models of sensitivity, as mentioned above, all fall under a general category of person-by-environment interactions that aim to explain individual differences in reactivity/responsivity/sensitivity to environmental influences, and may thus be considered models of environmental sensitivity (Pluess, 2015). However, a distinction is made in this thesis, and elsewhere (e.g. Pluess, 2015; Pluess et al., 2017), between the diathesis-stress model and the more recent models, due to two principle differences: a) differences in their proposed interaction pattern with the environment (fan shaped in diathesis-stress model vs. cross-over for the other three), and b) differential emphasis on the notion of vulnerability/sensitivity to risk (diathesis-stress model) versus general sensitivity to both risk and enrichment. Therefore, for the remainder of this thesis, ***differential susceptibility theories*** refer to differential susceptibility hypothesis, sensory processing sensitivity and biological sensitivity to context theories, all exemplified by

their core similarity with each other (i.e. cross-over interaction). The term ***environmental sensitivity*** is used to refer more broadly to individual differences in *general sensitivity to environmental influences of both negative and/or positive valence*.

Although there are differences in how differential susceptibility theories conceptualise and index environmental sensitivity (see **Sections 1.1.2** and **1.1.3**), they all suggest that individual differences in environmental sensitivity have a genetic basis. This proposition is supported by growing evidence from candidate gene studies showing that certain genetic variants moderate the impact of a large range of environmental influences in the proposed "*for better and for worse*" manner. Specifically, they have found that the same genotypes that are associated with worse outcomes in adverse contexts are also associated with better outcomes/no difference in risk in positive/low risk contexts. However, there remain certain limitations and gaps in research on genetic studies of environmental sensitivity. The main aim of this thesis was therefore to address some of the unknowns in the genetics of environmental sensitivity and its moderating effects on mental health outcomes. In this vein, three main goals were pursued. First, to develop and use a psychometrically valid measure of environmental sensitivity for children and adolescents, the main age group of the samples used in the current thesis. Second, to examine the proposed genetic basis of environmental sensitivity, by estimating its heritability for the first time, and exploring the molecular genetic factors associated with it, using candidate and genome-wide approaches. Third, to examine the effect of genetic sensitivity in susceptibility to psychological problems and response to psychological treatment, using longitudinal cohort, as well as, clinical samples.

This introductory chapter is organised into three sections. The first section describes the theoretical aspects of environmental sensitivity, starting with an overview of the differential susceptibility theories, including a review of the proposed mechanisms underlying variations in environmental sensitivity. The second section presents an overview of research in environmental sensitivity, followed by an evaluation of the limitations and gaps in current research on the genetics of environmental sensitivity. The third section details the aims of the current thesis as examined in each chapter.

1.1.1 The differential susceptibility theories

The **differential susceptibility hypothesis** (DS; Belsky, Bakermans-Kranenburg, et al., 2007; Belsky & Pluess, 2009, 2013a) postulates that individuals differ in the extent to which they are affected by environmental influences due to individual differences in *general* susceptibility—and not just vulnerability. Importantly, DS proposes that those individuals who are more susceptible to the effects of negative environments are also more sensitive to the beneficial effects of positive environmental exposures. The inherent general sensitivity thus functions in a "*for better and for worse*" manner (Belsky, Bakermans-Kranenburg, et al., 2007). DS was initially proposed on the basis of evolutionary theory, according to which the primary goal of all living beings is to pass on their genes to future generations. From this perspective, developmental strategies that enhance the chances of reproductive fitness are considered optimal even if they infer psychological maladjustment. For example, whereas heightened levels of aggression are considered maladaptive in most societies, an evolutionary-developmental view may suggest that aggression in a context of low resources may be an adaptive and optimal strategy that increases the chances of obtaining resources and, hence, promote reproductive fitness. Developmental plasticity/high sensitivity – the ability to adapt the phenotype to environmental conditions – may increase reproductive fitness through optimal adaptation to the prevailing context. However, since the future is inherently unpredictable, high sensitivity would not always prove to be adaptive—specifically in environments where the early environment is not predictive of what is to come. In addition, heightened sensitivity to contexts increases the probability of something going wrong in a more complex system that facilitates more interactions with environmental stimulations. Thus, higher sensitivity to environmental stimulations, or developmental plasticity, is associated with both risks and opportunities. Consequently, drawing on evolutionary theory, it is proposed that there should be variation in such environmental sensitivity, where natural selection would have led to propagation of at least two sensitivity types: high and low phenotypic sensitivity (Belsky, 1997b, 2005). Following on from this line of reasoning, DS maintains that individual differences in environmental sensitivity are predominantly genetically-determined; recently, however, it has been suggested that high susceptibility may also be shaped by early environmental influences (Pluess & Belsky, 2011).

Vulnerability, as captured in the diathesis-stress model, reflects the "dark side" of differential susceptibility. The term '*vantage sensitivity'*, on the other hand, has been

used to refer to the "bright side" of differential susceptibility (Pluess & Belsky, 2013a). Vantage sensitivity is the disproportionate advantage a highly susceptible individual may gain in the context of a supportive environment, as opposed to the disproportionate disadvantage in an adverse environment. Failure to benefit from positive environmental influences has been termed *vantage resistance*. Importantly, although vantage sensitivity describes primarily the positive end of differential susceptibility, in some cases a sensitive individual might be especially responsive to the effects of positive environments but not necessarily to the effects of negative environments. Similarly, a vantage-resistant individual may be resistant to the effects of positive environments but not necessarily resilient to the negative impact of adverse experiences.

The **biological sensitivity to context** (BSC; Boyce & Ellis, 2005; Ellis et al., 2005), similar to DS, suggests that some individuals are generally more, and others less, physiologically reactive to their environments; elevated reactivity is thought to moderate the outcomes of both 'positive' and 'negative' environmental exposures. Like DS, BSC is also concerned with development from an evolutionary perspective. However, the BSC model focuses mainly on 'conditional adaptation', proposing that individuals' degree of environmental sensitivity is dependent on the conditions of their specific context. Notably, BSC suggests that individual differences in physiological reactivity—reflected in stress-response systems—reflect individual differences in environmental sensitivity. According to this model, children in especially positive environmental contexts, as well as those in acute adverse conditions, will both develop higher physiological reactivity, a marker of high environmental sensitivity. Specifically, stressful childhood environments are thought to up-regulate biological sensitivity to adverse contexts in order to better detect and respond to future environmental threats; supportive early environments also up-regulate biological sensitivity, increasing their ability to benefit from the positive features of their environment. Environments that are not particularly adverse or supportive, on the other hand, down-regulate biological sensitivity to context, with physiological reactivity patterns that are less biased and less responsive to environmental influences, as is the case for the majority of individuals. Exploratory analyses of this model have supported the BSC model by showing that the lowest prevalence of highly reactive children were found in conditions of moderate stress, whereas higher prevalence-rates were found at both tails of the distribution of environmental quality (Ellis et al., 2005; Gunnar, Frenn, Wewerka, & Van Ryzin, 2009).

The **sensory processing sensitivity theory** (SPS; Aron & Aron, 1997) is also concerned with individual differences in environmental sensitivity. However, in contrast to DS and BSC, SPS was originally less concerned with developmental processes and more focused on explaining individual differences in sensory sensitivity and the depth of processing in adults. Most importantly, SPS theory approaches the notion of individual differences in environmental sensitivity from a personality perspective, suggesting that heightened environmental sensitivity is reflected in a highly sensitive personality type. SPS, similar to DS and BSC, proposes that individuals characterized as highly sensitive are more influenced by both negative and positive environmental influences. According to SPS, the highly sensitive personality trait is characterised by greater awareness of sensory stimulation, behavioural inhibition, higher emotional and physiological reactivity and deeper cognitive processing of environmental stimuli. Based on this concept of sensitivity, Aron and Aron (1997) have developed the *Highly Sensitive Person* (HSP) scale, which indexes an individual's propensity for higher sensitivity to their physical and psychological context (more details on the highly sensitive personality trait, the measure and relevant traits are presented in **Chapter 2**). High sensitivity is hypothesised to have a genetic basis and to emerge in infancy, but is further shaped by the environmental contexts that the individual is exposed to during early development (Aron & Aron, 1997; Aron, Aron, & Davies, 2005).

1.1.2 An integrated environmental sensitivity perspective

The three differential susceptibility theories each emphasise different aspects of sensitivity. Thus, the differential susceptibility hypothesis focuses on natural selection and individual differences in developmental processes; biological sensitivity to context focuses on conditional adaptation and variations in the HPA axis; and sensory processing sensitivity focuses on phenotypic manifestation of sensitivity and stable variations in processing of environmental stimuli.

Importantly, the three theoretical models reflect two distinct perspectives on individual differences in environmental sensitivity: one concerned with how environmental sensitivity is implicated in developmental processes, whilst the other conceptualises environmental sensitivity as a distinct phenotype. The developmental perspective is reflected in biological sensitivity to context and the differential susceptibility hypothesis. Both of these models are mainly concerned with the way environmental sensitivity operates in interaction with environmental influences to impact developmental outcomes (the 'operational' perspective). However, they do not provide

a phenotype of environmental sensitivity. For example, children characterised as having a more reactive temperament in infancy (a sensitivity marker) are shown to develop into children with consistently more or less aggression depending on the early care environment (Belsky & Pluess, 2012; Pluess & Belsky, 2009, 2010b). The SPS theory, on the other hand, considers environmental sensitivity as a relatively stable personality trait present across different contexts (Aron & Aron, 1997), allowing phenomenological exploration of environmental sensitivity, and examining its aetiology and nomological network as a psychological phenotype.

Accordingly, research exploring these different perspectives has tended to focus on different markers of sensitivity to examine the potential moderating effects of sensitivity on environmental influences. For example, researchers using the differential susceptibility hypothesis have mainly concentrated on infants' difficult temperament or specific genetic variants as markers of environmental sensitivity; those working under the BSC or SPS framework have, respectively, tended to focus on physiological reactivity and the highly sensitive personality trait as their sensitivity markers of choice.

Despite clear conceptual differences between the DS and BSC (Del Giudice, Ellis, & Shirtcliff, 2011) and SPS in how sensitivity is indexed in each model, it is possible to integrate all three, by considering that difficult temperament, certain genetic variants, physiological reactivity and highly sensitive personality all reflect environmental sensitivity at different levels of analysis (Pluess, 2015). For example, environmental sensitivity to the effects of parenting in predicting behavioural problems has been demonstrated as a function of children's sensitivity genotype (Lahey et al., 2011), difficult temperament (van Zeijl et al., 2007), physiological reactivity (El-Sheikh et al., 2009), and highly sensitive personality (Slagt, Dubas, van Aken, Ellis, & Deković, 2018). The moderating effect of these markers in a for better and for worse manner, therefore, has identified them as sensitivity markers at different levels of analysis, from the more distal genetic factors to the more proximal personality trait. Although these independent research findings suggest that these markers reflect the same underlying construct to different degrees, there is no empirical evidence linking these various markers of sensitivity. Further research is therefore required to determine whether a difficult temperament in infancy is associated with a highly sensitive personality in adulthood, or whether the same sensitivity genes are related to physiological or phenotypic markers of sensitivity.

All three of the models described above converge on three key aspects. Firstly, there

exist significant individual differences in general sensitivity to environmental influences. Second, this environmental sensitivity functions in a for better and for worse manner in moderating the outcomes of environmental influences; more sensitive individuals, compared to less sensitive ones, are at higher risk in adversity, but are more able to flourish in positive contexts. Thirdly, all three models suggest that individual differences in environmental sensitivity have a genetic basis. The next section details the specific underlying mechanisms proposed by each model in explaining environmental sensitivity.

1.1.3 Mechanisms of environmental sensitivity

The exact mechanisms of environmental sensitivity are currently unknown, though the three prominent differential susceptibility theories have proposed potential biological mechanisms. Sensory processing sensitivity theory (Aron & Aron, 1997) has suggested the brain regions/processes involved in awareness of and attention to subtle stimuli, emotional responsivity, empathy to others' affective cues, and depth of processing of the stimuli as the underlying mechanism of heightened sensitivity to environmental influences. Biological sensitivity to context proponents (Boyce & Ellis, 2005; Ellis et al., 2005) have emphasized the role of stress response systems such as autonomic, adrenocortical, or immune reactivity in response to psychosocial stressors, and propose that variations in such psychobiologic reactivity reflects individual differences in sensitivity/responsivity to environmental influences. Differential susceptibility hypothesis proponents (Belsky & Pluess, 2009) have mainly emphasized the involvement of dopaminergic and serotoninergic circuitry that is implicated in responsivity to reward and punishment, and amygdala reactivity as one of the several central nervous system mechanisms. Variations in these systems are suggested to relate to reward threshold, differences in attention, orientation of response, response regulation, and emotional reactivity, all-important domains in the extent of responsivity/reactivity to environmental stimuli.

Indeed, there is growing evidence to support the involvement of the various hypothesised systems in individual differences in environmental sensitivity. For example, Acevedo (2014) found that high sensitive individuals showed greater activation in regions of brain involved in attention and action planning, awareness, integration of sensory information, empathy (e.g. cingulate and premotor area [PMA], cingulate, insula, inferior frontal gyrus [IFG], middle temporal gyrus [MTG]), while viewing photos of their romantic partners and of strangers displaying positive, negative,

or neutral facial expressions. In another study, Jagiellowicz et al. (2011) found that high sensitive individuals showed stronger activation in visual processing and attention processing brain regions when they were tasked with noticing subtle differences in photographs of landscapes. Other studies have found that variations in serotoninergic and dopaminergic system genes are associated with individual differences in amygdala reactivity and toddler's salivary cortisol levels in response to environmental influences (Bakermans-Kranenburg, Van, Pijlman, Mesman, & Juffer, 2008; Munafo, Brown, & Hariri, 2008).

In an attempt to integrate the suggested mechanisms, Belsky and Pluess (2013a) have suggested that heightened environmental sensitivity may be the function of a generally more sensitive central nervous system. This heightened sensitivity of the central nervous system may be reflected in various biological, physiological and psychological markers found to increase sensitivity to both negative and positive aspects of the environment. According to this hypothesis of "neurosensitivity", genetic and environmental factors influence physiological structures and functions of organs, including the central nervous system, which may result in a brain that is generally more reactive to environmental influences.

1.2 Review of environmental sensitivity research

Depending on the research interests of the investigators, environmental sensitivity has been studied using genetic (e.g. serotonin transporter gene polymorphisms), physiological (e.g. cortisol reactivity) or psychological (e.g. infant temperament, highly sensitive personality) markers. In molecular genetics studies, associations between a genetic variant (sensitivity marker), an environmental variable (e.g. life events) and a psychological outcome (depression) are examined in so-called gene-environment interaction (GxE) studies. These studies usually test whether a given genetic marker moderates the association between an environmental variable and the psychological outcome in crossover interaction as would be expected based on theory. On the physiological level, skin conductance reactivity is used, for example, as a marker of environmental sensitivity, which has been found to moderate the relationship between marital conflict and child externalizing (El-Sheikh et al., 2009). On the psychological/behavioral level, environmental sensitivity has been tested, for example, as a function of infant temperament, which has been found to moderate the effects of maternal discipline on child externalizing behavior, for better and for worse (van Zeijl et al., 2007). Regardless of the selected sensitivity marker, the main purpose of most

research in the field has been to test the hypothesised crossover interaction pattern of general environmental sensitivity in response to various environmental influences, with much of the research finding consistent evidence in support of the theoretical proposition.

On the behavioral level, some of the most consistent evidence is found in developmental studies on parenting and infant temperament. Much of the research indicates that the negative emotional dimension of infant temperament moderates the effects of quality of care on various indices of children's psychosocial development (Dopkins Stright, Cranley Gallagher, & Kelley, 2008; Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011; Pluess & Belsky, 2010a, 2010b; Stright, Gallagher, & Kelley, 2008). Generally, children with more negative emotionality in infancy have been found to be more adversely affected by unresponsive parenting, as well as benefiting substantially more from responsive parenting, in comparison to those children with less negative emotionality (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010; Pluess & Belsky, 2009). In one of the largest of these studies (N = 1,259), Raver, Blair, and Willoughby (2012) examined the effects of chronic poverty and poverty-related risks, such as family financial strain and housing quality, and the moderating role of infant temperament, on variability in executive function. They found that, in children with a high reactive temperament, chronic exposure to financial strain was associated with lower executive function at 4 years, while lower exposure to financial strain was associated with higher executive functioning. For children with a low-reactive temperament, however, financial strain was not related to differences in executive functioning. Hence, the more reactive children were more affected by both high and low levels of financial strain, compared to children with a less reactive temperament. The effects were robust, even after controlling for demographic differences, including ethnicity, geographic location and mother's age and educational level.

Studies using the Highly Sensitive Person (HSP) scale (Aron & Aron, 1997) as a measure of sensitivity have evidenced similar interaction patterns. For example, in an experimental study by Aron et al. (2005), undergraduates were asked to complete a cognitive task, with participants being randomly assigned to a condition that either implied they were doing much better (low stress) or much worse than the peers sitting around them (high stress). Participants with high scores on the HSP scale reported more negative affect than others in the high stress condition, but also the least negative affect in the low stress condition. Those scoring low, on the other hand, did not differ

significantly in negative affect regardless of condition, suggesting they were generally less affected by their context. In another, recent study, Rubaltelli, Scrimin, Moscardino, Priolo, and Buodo (2018) examined whether exposure to terrorism-related pictures interacted with individual differences in HSP and psychophysiological response to stress (i.e. heart rate variability) to explain individuals' risk perception (i.e. perceived likelihood of a terrorist attack) and willingness to trade off one's privacy to increase national security. Participants were randomly assigned to one of the two conditions (terrorism-related vs. neutral pictures), with their risk perception being assessed after having watched the pictures. Results showed that terrorism risk-perception was moderated by psychophysiological reactivity to stress and willingness to trade off one's privacy to improve national security was moderated by HSP, with highly sensitive individuals particularly affected by terrorism‑related pictures. Similar interaction patterns have been found in studies with children (Nocentini, Menesini, & Pluess, 2018; Pluess & Boniwell, 2015; Slagt et al., 2018). Slagt et al. (2018) for example, in their longitudinal multi-informant study of 264 kindergarten children, found that highly sensitive children were more susceptible to changes in both negative and positive parenting in predicting externalizing behaviour.

Research concerning genetic markers of environmental sensitivity can be divided into two main groups. The first group includes early GxE studies, the results of which support the differential susceptibility theories, but which have not been conducted from the differential susceptibility perspective from the outset (e.g. Caspi et al., 2002; Caspi et al., 2003; Eley et al., 2004). The second group includes more recent GxE studies (from 2009 onwards), which have been conducted from the outset to test environmental sensitivity from a differential susceptibility perspective. The first group of studies have been used as initial evidence, supporting the rationale for the following, second group of studies. With regards to the first group of studies, Belsky and Pluess (2009) draw on evidence from GxE research to show that individual differences in sensitivity to environmental influences exist and that the same gene variants are associated with elevated response(s) to both positive and negative environmental influences. Importantly, they highlight that, whilst these GxE studies suggest, at first sight, that the examined candidate genes represent genetic vulnerability/risk factors for the development of psychiatric disorders in response to environmental adversity, it appears to have gone unnoticed that those individuals carrying the "risk" variant often show less negative outcomes compared to those without this variant in the absence of adversity.

For example, while the s-allele in the earliest GxE studies of *5-HTTLPR* by Caspi et al. (2003) and Eley et al. (2004) was associated with higher risk for depression in the context of stressful life events and adverse family environment, the same genotype also inferred lower risk of these problematic outcomes in the absence of stressful life events and family problems. A closer look at the GxE studies with *MAOA* (e.g. Caspi et al., 2002; Widom & Brzustowicz, 2006) showed a similar pattern: the putative vulnerability allele (i.e. low-*MAOA*-activity) infers high risk for conduct disorder/antisocial behaviour in the context of childhood maltreatment but lower risk in the absence of maltreatment.

It appears that the evolutionary perspective of differential susceptibility theories may also be better able to account for the observation that many of the genetic variants studied in candidate GxE psychiatric studies are "common" variants (i.e. they have a high frequency in the general population). If there were gene variants that are associated exclusively with an increased risk for the development of psychopathology when faced with adversity, one would expect that the frequency of these genes would decrease over time (and that the gene variants associated with resilience would increase). However, the observation that many of these genes are common, with some even appearing to be under positive selection (Ding et al., 2002), suggests that these gene variants may have benefits that counteract the negative effects of heightened vulnerability; an observation that is more in line with general susceptibility to context, rather than mere vulnerability (Belsky & Pluess, 2009; Pluess & Belsky, 2013a).

The second group of studies conducted under the differential susceptibility framework, have often supported the notion of general sensitivity (For meta-analyses of these studies, see: Bakermans-Kranenburg & van IJzendoorn, 2011; van IJzendoorn, M. H., Belsky, J., & Bakermans-Kranenburg, M. J., 2012). For example, the *5-HTTLPR* s-allele has been found to moderate *for better and for worse*, the impact of perceived racial discrimination and child maltreatment on conduct problems and antisocial behaviour (Cicchetti, Rogosch, & Thibodeau, 2012). With regards to *COMT*, Baumann et al. (2013) found, in their sample of 782 adults, that *COMT* Val158Met genotype moderated the effects of childhood adverse experiences on anxiety sensitivity in adulthood, with the Met allele inferring greater risk of anxiety for those who were exposed to adverse experiences but also lower scores in the absence of such events. The proposition that these, and many other candidate genes (For a review, see Belsky & Pluess, 2009, 2013a), reflect general sensitivity to environmental influences is further

supported by studies showing that these genes moderate the influence of a large range of environmental effects that are relevant to *normal development*. For example, *5-HTTLPR* has been found to moderate, *for better and for worse*, the impact of maternal responsiveness on children's moral development (Kochanska, Kim, Barry, & Philibert, 2011), the effect of parenting practices on children's positive affect (Hankin et al., 2011) and perceived racial discrimination and maltreatment on children's behavioural conduct (Cicchetti et al., 2012). Similarly, the *DRD4* 7-repeat variant has been found to be associated, *for better and for worse*, with variations in attention in the context of early maternal care (Berry, Deater-Deckard, McCartney, Wang, & Petrill, 2013), the development of social competence in the context of quality of child-care (Belsky & Pluess, 2013b), pre-schoolers' enhanced literacy following a literacy improvement programme (Kegel, Bus, & van Ijzendoorn, 2011) and pro-social behaviour in the context of parenting quality (Knafo, Israel, & Ebstein, 2011).

Furthermore, experimental GxE studies, in which response to manipulations in environmental contexts or exposures (e.g. interventions to enhance parenting skills or therapeutic interventions) is examined as a function of genotype, show results consistent with differential susceptibility theories (For meta-analysis see: van Ijzendoorn & Bakermans-Kranenburg, 2015). Bakermans-Kranenburg et al. (2008) provided video-feedback to mothers on their parenting practices as part of a randomised intervention to promote sensitive parenting to mothers of 1-3-year-olds scoring highly for externalizing problems. They found that the intervention effect led to improvements in child behavior, but only for those children carrying the *DRD4* 7-repeat allele.

Other, more recent studies, embracing the shift in the psychiatric genetic field by examining the cumulative effects of several to thousands, rather than single candidate genes (polygenic score) in GxE designs, have found similar results. For instance, evidence from studies using multiple-gene composites have shown that genetic sensitivity moderates the links between sexual abuse and adolescent depression/anxiety (Cicchetti, Rogosch, & Sturge-Apple, 2007), family environment hostility/support and aggression in early adulthood (Simons et al., 2011) and parenting and adolescent self-control (Belsky & Beaver, 2011). It must be noted that, although these recent studies, using a polygenic approach, capture more of the variation in genetic sensitivity, they still rely on just a few selected candidate genes, typically less than 10 variants. In light of the widely-acknowledged limitations of candidate GxE approaches (e.g. selecting candidate genes without sufficient knowledge of the biological mechanisms of the

studied phenotype), the psychiatric genetic field has moved on to examining genetic associations using hypothesis-free approaches, such as genome-wide association studies (GWAS), genome-wide-environment interaction study (GWEIS) and Polygenic Score-Environment interactions (PGSxE). However, these genome-wide approaches have not yet been commonly applied in studies of environmental sensitivity, with only one study to date having used the PGSxE approach to conduct an a-priori test of the differential susceptibility hypothesis. In this study, using a genome-wide polygenic score of sensitivity, Keers et al. (2016) examined if higher sensitivity was associated with differential response to CBT treatment in a sample of 1000 children diagnosed with a range of anxiety disorders. They found that, consistent with theory, the more genetically sensitive children showed more discriminate response to the type of therapeutic treatment they received, compared to those who were less genetically sensitive.

It is important to note that, although a large number of empirical studies support the notion of individual differences in environmental sensitivity, not all a-priori studies of differential susceptibility theories provide evidence consistent with its predictions (see, e.g., for genetic studies: Cicchetti et al., 2012; Felmingham, Dobson-Stone, Schofield, Quirk, & Bryant, 2013). These contradictory findings may partly reflect the conceptual and methodological limitations of candidate GxE studies, which are discussed in the following sections.

1.2.1 Evaluation of findings in environmental sensitivity research

Environmental sensitivity research conducted from the perspective of differential susceptibility theories provides empirical support for the hypothesised crossover interaction pattern of general environmental sensitivity in response to environmental influences. GxE research conducted or interpreted from a differential susceptibility perspective also suggests that many of the so-called genetic vulnerability variants reflect sensitivity to both risk and enrichment, since they are associated with increased risk of psychopathology in response to environmental stressors, but also enhanced benefits in the context of positive environmental exposure or the absence of risk. Hence, it may be more appropriate to consider these variants as markers of sensitivity to environmental influences rather than mere risk factors for psychopathology (Belsky et al., 2009; Rutter, 2012). This view, of course, does not negate the possibility that some of these gene variants infer risk in specific contexts for some domains of functioning, or the existence of other variants that exclusively increase vulnerability for disorders without inferring advantages in positive environmental contexts (diathesis-stress interaction

model). The research findings, at the very least, call for questioning the implicit assumption underlying the majority of GxE studies in the psychiatric genetic field, and the interpretation of results solely from a diathesis-stress perspective.

Whilst the research evidence has, to date, addressed the main theoretical proposition of differential susceptibility theories, i.e. the cross-over interaction pattern, there are several areas of research that are yet to be explored and which are important caveats for understanding environmental sensitivity. Firstly, whilst research indicates that elevated sensitivity moderates the impact of a wide range of environmental influences on a variety of developmental outcomes, it is currently not clear whether this can be interpreted to mean that highly sensitive individuals are responsive/reactive to *all* environmental inputs and with respect to *any and all* developmental outcomes. In other words, is general sensitivity domain-specific or domain-general (Belsky, Bakermans-Kranenburg, et al., 2007)? The difficulty in answering this question is partly due to the fact that most research has examined specific environmental factors in the context of specific disorders (e.g. stressful life events in response to depression), and within GxE studies, certain genetic factors are commonly studied in relation to specific outcomes (e.g. *5-HTTLPR* and depression). Using a phenotype of sensitivity, such as highly sensitive personality, that reflects an individual's general tendencies for sensitivity to environmental influences, may provide a step forward in testing this question, though research using this approach is too sparse still to make inferences at this stage.

Secondly, the cross-sectional nature of all of the differential susceptibility-related work cited herein essentially presumes that children and adults who share the same sensitivity characteristics, be they temperamental, physiological or genetic plasticity factors, would function in a manner opposite to what was observed were they also observed under contrasting conditions. In order to empirically assert this assumption, longitudinal studies with repeated measurement of environmental contexts, sensitivity and outcomes are required; none currently exist, however.

Thirdly, notwithstanding the contribution of the large body of research conducted on environmental sensitivity since the publication of the first SPS, DS and BSC papers in the late 1990s, our understanding of the aetiology of general sensitivity to environmental influences as a phenotype remains limited. This is because most research inspired by these concepts has been, and still is, examining the main assertion of DS, which posits that inherent general sensitivity to environmental influences functions in a *for better and for worse* manner, such that sensitivity to the effects of environmental

influences can be extended from negative environments to positive ones. While the results of these studies provide strong support for the existence of individual differences in general environmental sensitivity, and how it may moderate a range of outcomes, they are not specially informative with regards to the underlying factors that contribute to variations in the phenotype of sensitivity, other than indicating that genetic factors may play a role in its aetiology.

The gap in research on genetics of environmental sensitivity is an important area of research worthy of further investigation. A better understanding of the aetiology of environmental sensitivity, its genetic architecture and which genetic variants contribute to individual differences in this trait are essential first steps in elucidating the biological mechanisms. Additionally, it is also important to explore how these genetically driven differences may impact the trajectory of mental health outcomes in response to environmental influences. Accordingly, the main aim of this thesis is to examine some of the 'unknowns' in the genetics of environmental sensitivity; the next section specifically focuses on the discussion of the unknowns and limitations of research in this area.

1.2.2 Limitations and current gaps in research on the genetics of environmental sensitivity

As noted in the previous section, there are many unknowns in the environmental sensitivity research – such as the exact mechanism of sensitivity, domain-specificity versus a domain-general nature of sensitivity and the aetiology of environmental sensitivity. Five main limitations and gaps in the research have been identified, which the present thesis intends to address empirically.

First, one of the main contentions of the differential susceptibility hypothesis, and at the core of its evolutionary rationale, is that individual differences in sensitivity have a genetic basis. Indeed, GxE research assumes this to be the case, by showing that the genes in these studies reflect variations in sensitivity to environmental influences. However, **no studies to date have examined the heritability of environmental sensitivity.** Heritability estimates indicate to what extent variations in a trait are due to genetic or environmental factors. In the absence of such research, it is impossible to determine how important genetic factors are for individual differences in general sensitivity to environmental influences, and if sensitivity is mainly a function of additive or dominant genetic effects, for example. In addition, it is currently unclear to

what extent the genetic factors underlying environmental sensitivity are different or similar to the ones underlying other, related traits. This is of particular interest because of the observed genetic correlation between comorbid disorders and correlated traits (Cross-Disorder Group of the Psychiatric Genomics, 2013; Trouton, Spinath, & Plomin, 2002; Waszczuk et al., 2015). Although previous studies of the highly sensitive personality trait have shown consistent correlations with other personality traits, such as neuroticism and extraversion (Smolewska, McCabe, & Woody, 2006; Sobocko & Zelenski, 2015), and depressive symptoms (Aron et al., 2005; Liss, Timmel, Baxley, & Killingsworth, 2005), no studies to date have examined their shared aetiology.

Second, all genetic studies of environmental sensitivity so far have used an operational view of sensitivity, wherein sensitivity is implied through a genetic variant's observed interaction pattern with the environment. Although the results may implicate these candidate genes as relevant to the aetiology of environmental sensitivity, **no studies to date have examined how these candidate sensitivity genes relate to the phenotype of environmental sensitivity** (i.e. highly sensitive personality trait). This is an important gap in research, because it cannot be assumed that the genes involved in response to the specific range of environmental factors currently studied are the same ones that contribute to significant variations in the phenotype of general sensitivity to all environmental influences. Specifically, as noted earlier, much of the currently nominated sensitivity genes have been studied within specific outcomes (e.g. *DRD4* and ADHD, *5-HTTLPR* and depression), and therefore may reflect specific sensitivities in response to specific events, rather than general sensitivity to contexts, as differential susceptibility theories propose. The empirical question therefore remains as to which genetic factors contribute to the observed individual differences in environmental sensitivity.

Third, despite research in the field of psychiatric genetics having moved on to exploratory genome-wide examination of genetic associations, **the entirety of environmental sensitivity genetic research is based on candidate gene approaches, rather than genome-wide methodology** (with the exception of a recent study by Keers et al. (2016)). This is despite the known limitations of a candidate gene approach. Specifically, while the main requirement of a candidate gene approach is the selection of candidate genes based on their biological relevance to the trait, current knowledge regarding the specific biological mechanisms underlying complex psychological traits including sensitivity remains limited. This is an important limitation, especially for

candidate gene research in environmental sensitivity, whereby the initial sensitivity genes have been identified based on their interaction pattern with environmental factors, rather than biologically established mechanisms underlying the trait as a first step (e.g. see: Belsky & Pluess, 2009, 2013a). Relatedly, research in the field of molecular genetics suggests that common traits are usually influenced by many thousands of gene variants, each of very small effect, rather than by a few variants of large effect (Culverhouse et al., 2017; Manolio et al., 2009). In other words, the genetic architecture of common behavioural traits are highly complex and polygenic (Donnelly, 2008). In addition, most genetic studies of environmental sensitivity have examined SNP level variations, rather than considering other units of genetic differences, such as at the gene-level or the gene-system level. This rather new approach in the field of psychiatric genetics allows the examination of genetic differences at a level more proximal to the biological differences underlying traits.

Fourth, while environmental sensitivity GxE research has examined a range of mental health outcomes, **very few have investigated the role of environmental sensitivity in predicting *clinical disorders* in response to relevant environmental risk factors.** The same paucity of research is observed when examining experimental/treatment response studies of environmental sensitivity and clinically diagnosed outcomes. It is therefore difficult to ascertain, by looking at current research using disorder symptoms, whether or not the same trajectories are to be expected with regards to clinically diagnosed disorders. This is an important gap in research, considering the debate on how common psychiatric disorders should be best defined: as extreme ends of a normally distributed phenotype (e.g. depression symptoms) or qualitatively distinct phenotypes (Kendell & Jablensky, 2003; Widiger & Simonsen, 2005). Genetic research suggests that qualitative disorders can be interpreted simply as being the extremes of quantitative dimensions (Plomin, Haworth, & Davis, 2009). Regardless of the specific perspective, both concepts of disorder make a distinction between extreme versus average symptoms, occurring, respectively, in the clinical population versus the general, non-clinical population. Whilst genetic sensitivity, in its interaction with adverse environmental factors, seems to contribute to variations in the 'middle section' of a quantitatively defined disorder, it may not explain variations at the extreme ends of this distribution. It is possible that elevated sensitivity in adverse contexts impairs functioning to some extent, but not to the extent that would contribute to the development of qualitatively different outcomes, i.e. clinical diagnosis. In order to be able to extend the relevance of sensitivity to psychopathology, empirical tests of its

association with clinically diagnosed disorders are essential. In addition, all GxE studies of environmental sensitivity to date have used candidate sensitivity genes in their design, rather than Genome-wide nominated or the polygenic score of a phenotype of sensitivity in predicting susceptibility to clinical disorder or treatment response; an important gap in research considering the previously-discussed polygenic nature of complex traits and using a phenotype of general sensitivity.

Fifth, **there are to date to no life-span studies of sensitivity**, only cross-sectional and limited longitudinal data; no existing studies span across multiple developmental stages of childhood, adolescence and adulthood. Research has consistently shown the negative impact of early adverse environmental influences to stretch beyond childhood and into adulthood and old age; yet it is unclear how individual differences in environmental sensitivity may moderate these effects at different developmental stages. This is an important consideration, not only for environmental sensitivity but for other GxE studies, because the effects of environmental and genetic factors on an outcome may differ as a function of the interaction between the two, but also as a function of developmental stage. Specifically, should we expect that the interaction between genetic sensitivity and environmental influences in childhood to infer a *for better and for worse* outcome throughout the life span, or do these effects change? Since environmental sensitivity has not been studied longitudinally from a life-span perspective, it is currently impossible to determine which model may best represent its function.

1.3 The aims of the thesis

The main aims of this thesis are to i) investigate the genetic basis of environmental sensitivity, by examining its heritability; ii) identify genetic variants related to individual differences in environmental sensitivity; and iii) examine how genetic sensitivity may be implicated in mental health outcomes via its interaction with environmental influences. The hypotheses are guided by both the theoretical propositions of the differential susceptibility theories, as well as current research in the field. The aims of the current thesis were examined using secondary data analysis; no data were collected by the author personally. The scope of the thesis and the planned analyses therefore had to take into consideration access to and availability of the data. The analytical approaches include a range of quantitative and molecular genetic methodologies as appropriate to the aims of each study, and included twin models to derive heritability estimates, candidate gene association study, GWAS, gene-based and polygenic score analysis. Psychometric analyses were also conducted to develop the

phenotypic measure of environmental sensitivity for use with children and adolescents.

Chapter 2 aimed to develop a new developmentally-appropriate measure of highly sensitive personality for use with children and adolescents, an age group that comprise the majority of the samples used in the current thesis. This was an important first step, because currently the only available measure is for use with adults only. The development and validation of the new scale was conducted via a large, multi-site study in the UK, comprising four independent samples (*N*= 1,931). The validation process included first selecting developmentally-appropriate items that capture the highly sensitive personality concept in line with the equivalent adult measure and confirming this via principal component and confirmatory factor analyses; second, establishing the construct validity of the new scale via examining its associations with other relevant constructs, personality traits and phenotypes; third, examining the reliability of the scale via test-re-test; and finally, examining the factor structure and associations with expected outcomes in another, independent sample. The resulting Highly Sensitive Child (HSC) scale was then used to index environmental sensitivity in the subsequent chapters. The analyses and results in this chapter address a gap in the current research into environmental sensitivity, by providing a valid measure of sensitivity in adolescents and children, facilitating future research within this age group.

Chapter 3 aimed to examine the hypothesised genetic basis of sensitivity, by investigating, for the first time, the heritability of environmental sensitivity. Heritability estimates were obtained by using classical twin design in a large sample of twins from the UK (*N*= 2,868). In addition to examining the heritability of environmental sensitivity, multivariate twin analyses were conducted to explore the genetic architecture of sensitivity: first, the genetic overlap between the three factors of the sensitivity scale were examined in order to determine whether the genetic basis of sensitivity is comprised of three correlated but rather distinct components, reflecting its factor structure; second, the genetic overlap between sensitivity, the Big Five personality traits, depression and anxiety were examined, in order to determine the extent of shared genetic aetiology between environmental sensitivity and these other related phenotypes. The analyses reported in this chapter address the current gap in research on environmental sensitivity, by providing the first heritability estimate for environmental sensitivity, as well as providing an indication of its genetic architecture and how its aetiology relates to other traits and outcomes.

Chapter 4 aimed to identify the molecular genetic factors associated with individual differences in environmental sensitivity. This was done via analysis of molecular genetic data and the HSC measure in three independent adolescent samples from the UK (*N*= 395 and *N*= 642) and Belgium (*N*= 913), using two main methodological approaches. In the first part, a candidate gene approach was taken, to examine the associations between environmental sensitivity and candidate sensitivity genes identified in the literature. The associations were examined from a single nucleotide polymorphism level of variation, as well as variations at gene level. In the second part, an exploratory, genome-wide approach was taken: first, GWAS was conducted on two independent samples, followed by meta-analysis of the results, in order to identify SNPs significantly associated with environmental sensitivity. These analyses were then followed up by genome-wide, gene-level and system-level association analysis. Finally, polygenic score analyses were conducted to predict sensitivity across the two independent samples, as well as using a cross-trait approach, by using publically available summary statistics data from large GWAS of thirteen other phenotypes relevant to environmental sensitivity. The analyses in this chapter address the main limitations of genetic studies of sensitivity to date, by examining the candidate genetic associations with the phenotype of environmental sensitivity and also conducting the first exploratory genome-wide search for genetic variants and biological pathways associated with this trait.

Chapter 5 aimed to investigate the impact of genetic sensitivity on mental health in response to environmental influences. This was done via three separate studies, each examining genetic sensitivity-x-environment interactions, using the polygenic scores of sensitivity obtained in the previous chapter. The first study includes longitudinal data for 2,863 individuals from a prospective longitudinal cohort study from the UK, and examined, for the first time, the interaction between a polygenic score of sensitivity and quality of psychosocial environment in childhood in predicting psychological distress across life span (ages 7 to 50). The second study used cross-sectional data to examine the interaction between the polygenic score of sensitivity and childhood maltreatment, and stressful life events, in the prediction of clinical depression case/control status in a sample of 2,434 adults. The third study included cross-sectional data from a clinical trial study of response to CBT treatment for paediatric anxiety disorders. This study examined whether and how genetic sensitivity moderated response to the three different types of Cognitive Behavioural Therapy (CBT) treatment (individual CBT, group CBT, guided self-help CBT) in a sample of 913 children with clinically-diagnosed anxiety

disorders. The analyses in this chapter address the main limitations of previous GxE studies by using a polygenic score of sensitivity, rather than relying on candidate genes as an index of genetic sensitivity. In addition, each study addresses other specific limitations: the first study addresses the current gap in research on the impact of genetic sensitivity across life-span, of which there are no studies to date; the second study addresses the gap in research on the relevance of environmental sensitivity to clinical disorders (i.e. major depression), where the majority of current studies have used symptoms rather than clinical diagnosis outcomes; the third study examines treatment response to intervention, using a polygenic score of sensitivity derived from a phenotype of sensitivity that represents general sensitivity to contexts.

Chapter 6 provides an overview of the results of empirical investigations in this thesis and offers a discussion on the findings in the context of the stated aims of this chapter. The findings are also interpreted for their implications for research on environmental sensitivity, as well as in the wider field of psychiatric genetics.

Chapter 2

Development and psychometric validation of a measure of environmental sensitivity for use with children and adolescents: the Highly Sensitive Child scale

2.1 Introduction

The three differential susceptibility theories (i.e. sensory processing sensitvity: Aron & Aron, 1997; differential susceptibility hypothesis: Belsky & Pluess, 2009; biological sensitivity to context: Boyce & Ellis, 2005) all suggest that individuals differ in their general sensitivity to environmental influences. According to these theories, heightened sensitivity to environmental exposures is not, in and by itself, a marker of vulnerability. Instead, it reflects the inherent tendency for greater sensitivity to environmental influences. These theoretical models propose that high sensitivity functions in a *for better and for worse* manner, such that it infers higher risk for negative outcomes in the context of adversity, but also renders the individual more susceptible to profit from the beneficial features of positive environmental influences. As detailed in **Chapter 1**, the three different susceptibility theories have proposed and studied different markers of environmental sensitivity. For example the differential susceptibility hypothesis emphasises genetic factors and infant temperament, while biological sensitivity to context focuses on physiological markers such as stress-reactivity. Research evidence reviewed in **Chapter 1** suggests that these markers reflect variations in response/reactivity to a large range of environmental influences, consistent with the proposed *for better and for worse* interaction pattern. However, none of these markers provide a quantifiable measure of inter-individual differences in general levels of sensitivity to environmental influences, in other words, a phenotype of environmental sensitivity. This is an important consideration, since quantification of individual differences in environmental sensitivity on a population level, studying its nomological network, and understanding its biological underpinnings require a phenomenologically ascertained measurable phenotype. The sensory processing sensitivity theory by Aron and Aron (1997) does exactly this: exploring, formulating and providing a phenotypic measure of environmental sensitivity via the Highly Sensitive Person scale (HSP; Aron & Aron, 1997).

While the HSP scale has been considered and studied as a promising phenotype of environmental sensitivity in adults (see **Chapter 1**), there is currently no validated self-report measure for use with children and adolescents. The main aim of the current chapter was therefore to report on the development and psychometric properties of a new measure of environmental sensitivity, based on HSP, for use with children and adolescents. Developing a valid measure of environmental sensitivity for this developmental stage is an important first step towards the main aim of this thesis,

because the data used throughout this thesis comprises of children and adolescent samples. Having a developmentally appropriate measure of environmental sensitivity is a fundamental prerequisite in order to be able to estimate the heritability of this trait and identify the molecular genetic factors in subsequent chapters.

The remainder of the introduction to this chapter is organised in three main parts. The first part includes an overview of sensory processing sensitivity theory and a detailed description of the conceptualisation of the underlying highly sensitive personality trait. The second part includes a review of empirical research on this phenotype and examines how it relates to other traits and outcomes. The third part summarises the specific aims of the presented analyses.

2.1.1 The sensory processing sensitivity theory and the highly sensitive personality trait

Sensory processing sensitivity theory was put forward by Aron and Aron (1997) based on their observations in clinical settings, of some individuals exhibiting generally higher sensitivity to environmental influences, a specific pattern of responsivity to emotional and physical environmental stimuli consistent with Jung's concept of innate sensitiveness (Aron, 2004). In their seminal paper, Aron and Aron (1997) describe a subset of individuals, termed highly sensitive persons, who tend to be generally more affected by their environmental context as a function of differences in sensory processing sensitivity, characterised by (a) greater awareness of sensory stimulation, (b) behavioural inhibition (c) deeper cognitive processing of environmental stimuli, and (d) higher emotional and physiological reactivity (Aron, Aron, & Jagiellowicz, 2012). These characteristics may manifest as psychological and behavioural tendencies such as lower threshold for reactivity to stimuli, being easily overwhelmed by sensory and psychological stimuli, pausing to reflect when faced with novel situations, greater attention to detail, and greater intensity in feelings of pleasure or discomfort. Aron and Aron (1997) suggest that the tendency for a lower threshold of reactivity to sensory stimuli and higher attention capture by a larger number of salient stimuli, results in a larger processing load that may lead to overstimulation and temporary pauses and behavioural inhibition, and a more complex and discriminating stimuli-processing style that results in deeper processing of emotions and cognitions (i.e. more reflective).

The tendency to inhibit response in the face of novel stimuli or uncertainty, by pausing and evaluating information prior to initiating behaviour is suggested to reflect the

function of the behavioural inhibition system (BIS) and the behavioural activation systems (BAS) (McNaughton & Gray, 2000). While BAS is the source of goal-directed behaviour, and reflects sensitivity to conditioned and unconditioned signals of reward, BIS reflects sensitivity to punishment, non-reward and novelty (Carver & White, 1994). Aron and Aron (1997) argue that a highly sensitive person's behavioural inhibition due to high levels of physiological arousal in novel situations, reflects the BIS.

Aron and Aron (1997) also suggested that the highly sensitive personality is reflected in, and sometimes masked by, what other researchers call inhibitedness in children (e.g. Kagan, Reznick, & Snidman, 1988), introversion in adults (e.g. Eysenck, 1990; Stelmack, 1990), innate shyness (e.g. Cheek & Buss, 1981; Daniels & Plomin, 1985), and reactivity (Rothbart, 1989; Strelau, 1983). Specifically, it is suggested that low sociability (including inhibitedness, introversion, shyness) and negative affect (including neuroticism, anxiety) are characteristics that may be emphasised in highly sensitive individuals (Aron et al., 2005). They reason, that this is because sensory processing sensitivity can, in some highly sensitive individuals, manifest itself as low sociability and neuroticism, with the former as a strategy to avoid overstimulation and the latter as a consequence of the interaction between sensitivity and aversive experiences. Specifically, it is proposed that while low sociability can be a consequence of aversive social and attachment experiences, it can also be a consequence of high sensitivity, whereby low sociability develops over time as an adaptive response to avoid overstimulation. This is because the social situations most associated with shyness/introversion, such as groups and meeting strangers, can be highly stimulating contexts due to their aspects of novelty, unpredictability and complexity. Higher arousal due to higher sensitivity to stimulation may overwhelm the individual and lead to poor performance in such situation, leading to discomfort in and avoidance of social situations. High sensitivity in the contexts of adverse environmental experiences can lead to neuroticism/negative affect/anxiety, since highly sensitive persons experience the same adverse environment as more negative, and retrospective evaluations of the negative experience is conducted more deeply and in greater detail. This can lead to greater awareness of potential threat cues in prospective evaluation of danger and ensuing preoccupation with danger and mitigating actions, resulting in chronic anxiety, negative effect and introversion.

Aron and Aron (1997) developed a 27-item self-report questionnaire, the Highly Sensitive Person scale (HSP; Aron & Aron, 1997), to index the core features of highly

sensitive personality, as a function of variations in threshold of sensory stimulation (e.g. being easily startled by louse noises), and depth and breadth of processing of sensory and emotional stimuli (overwhelmed when having a lot going on, attention to detail, intensity of pleasure and discomfort). (See **Appendix 2.1** for the HSP questionnaire). The development of the scale included a qualitative study with interviews of self-identified highly sensitive individuals to examine the subjective phenomenon, followed by six studies that included quantitative psychometric analyses of the scale in order to establish its convergent and divergent validity by examining its associations with the hypothesised traits and outcomes (Aron & Aron, 1997).

2.1.2 The highly sensitive personality and its association with other traits

HSP has since been examined in a range of studies using both correlational and experimental designs, including brain-imaging studies. The results confirm the theoretical proposition that highly sensitive individuals are generally more sensitive to their environmental contexts compared to less sensitive individuals, and that this sensitivity is exhibited in response to both negative and positive influences.

For example, in a behavioural experiment, Aron et al. (2005) assigned undergraduates randomly to a situation that either implied they were doing much better or much worse than their peers when performing a cognitive task. Participants with higher scores on an abbreviated version of the HSP scale reported more negative affect than others after the task if they were led to believe they did worse than others, but also the least negative affect in the condition where they were led to believe they had done better. Those scoring low, on the other hand, did not differ significantly in negative affect regardless of condition, suggesting they were generally less affected by the experimental manipulation. Other research has shown that higher scores on the HSP scale are associated with higher risk for adult depression and negative emotionality following adverse childhood experiences, but also lower risk for such problems in response to more favourable childhood contexts (Aron et al., 2005; Liss et al., 2005). More recently, Booth, Standage, and Fox (2015b) tested in a cross-sectional study whether scores on the HSP scale in adulthood moderated the effects of retrospectively reported childhood experiences on adult life satisfaction. They found a significant interaction, suggesting that more sensitive individuals were more negatively affected by negative childhood experiences compared to less sensitive individuals. In another study, Jagiellowicz, Aron, and Aron (2016) examined the valence and arousal levels of individuals rating high or low on the HSP scale (25 percentile), when viewing emotionally evocative

(positive, negative) and neutral pictures. They found that highly sensitive individuals (compared to low sensitive) rated emotional pictures, especially positive ones, as significantly more intense. More specifically, the arousal in response to positive pictures was greater for highly sensitive individuals (vs. low) if they had reported a history of high-quality parenting as children.

Adding further evidence to the validity of the scale, is research applying fMRI methodology to investigate the link between HSP and variations in brain activity in response to environmental stimulations. These studies provide evidence that higher scores on the HSP scale are associated with an increased neuronal responses to subtle changes in visual scenes (Gerstenberg, 2012; Jagiellowicz et al., 2011), greater neuronal activity in regions associated with attention and working memory in a task requiring attending to context to visual scenery (Aron et al., 2010), and stronger activation of brain regions involved in sensory integration, awareness, empathy, and self-other processing in response to positive, negative, or neutral facial expressions (Acevedo, Bianca P. et al., 2014). In a follow up study on the results of an earlier behavioural experiment by Jagiellowicz et al. (2016), Acevedo, Jagiellowicz, Aron, Marhenke, and Aron (2017) examined if the reactivity to emotionally evocative positive and negative, or neutral images was associated with variations in brain activity for high versus low sensitive individuals. They found that for all images, highly sensitive individuals (vs. low), showed more activation in areas of brain associated with emotional memory processing, learning, physiological regulation, awareness, reflective thinking, and integration of information (e.g. hippocampus, entorhinal area, hypothalamus, and temporal/parietal areas) and greater activation in areas involved in reward processing (ventral tegmental area, substantia nigra, caudate), self-other integration (insula and inferior frontal gyrus), calm (periaqueductal gray), and satiation (subcallosal anterior cingulate) for positive images. When viewing negative images, having experienced higher quality parenting in childhood was associated with more activation in areas involved in emotional regulation and self-control in highly (vs. low) sensitive individuals, indicating highly sensitive persons are more sensitive to the effect of quality of childhood parenting. Although the sample sizes in brain imaging studies are typically small ($N < 50$), these studies provide preliminary evidence for the proposed differences in the processing of environmental stimuli in high versus low sensitive individuals. Considering these studies alongside other behavioural studies, the findings suggest that the HSP scale captures the tendency to be generally more affected by the environmental context, as would be expected from the differential susceptibility

theories.

Although Aron and Aron (1997) conceptualised the HSP measure as reflecting a single factor, recent factor analyses in several independent samples (Booth et al., 2015b; Liss, Mailloux, & Erchull, 2008; Smolewska et al., 2006; Sobocko & Zelenski, 2015) revealed three distinct components underlying the HSP scale, which have been labeled by Smolewska et al. (2006) *Ease of Excitation* (EOE), *Aesthetic Sensitivity* (AES), and *Low Sensory Threshold* (LST). The EOE factor is represented by items that relate to being easily overwhelmed by external stimuli (e.g. "finding it unpleasant to have a lot going on at once "). LST is reflected in items that relate to unpleasant sensory arousal (e.g. "being easily overwhelmed by things like bright lights, strong smells, coarse fabrics, or sirens close by"). Finally, AES is represented by items that relate to aesthetic awareness (e.g. "being aware of subtleties in your environment" and "being deeply moved by the arts or music"). All three components tend to be positively correlated with each other, although to different degrees, with relatively high correlations between EOE and LST (ranging from r = .60 to .73), and more modest correlations between AES - LST (ranging from r = .17 to .45) and AES - EOE (ranging from r = .24 to .40) (Booth et al., 2015b; Smolewska et al., 2006; Sobocko & Zelenski, 2015). Smolewska et al. (2006) investigated correlations between the HSP scale and personality measures in adults, including the Big Five personality traits and BIS/BAS scales by Carver and White (1994), and found that the HSP total score was significantly and positively correlated with neuroticism (r = .45) and openness (r = .19), as well as both BIS (r = .32) and BAS (r = .16 for the reward-responsiveness subscale). When investigating associations with the three HSP subscales, they found that while neuroticism and BIS were correlated with all three factors, openness had a significant association only with aesthetic sensitivity (r = .37), low sensory threshold with lower extraversion (r = -.12), and ease of excitation, and aesthetic sensitivity with the BAS reward-responsiveness scale (r = .19 and r = .18, respectively) (for similar findings, see Gerstenberg, 2012). At first sight this correlation pattern appears to suggest that aesthetic sensitivity may reflect environmental sensitivity to more positive experiences, whereas ease of excitation and low sensory threshold reflect sensitivity to more negative experiences (Smolewska et al., 2006; Sobocko & Zelenski, 2015).

2.1.3 Aims

The main aim of the study was to develop a new measure of highly sensitive personality appropriate for use with children and adolescents based on the original HSP scale, and establish its psychometric properties in independent samples. This was done through four studies across four independent samples of children and adolescents from the UK, ranging in age from 8-19 years (total sample N = 1,931). Study 1 describes the creation of a 12-item scale, from a pool of 38 self-report questions, using a sample of 334 children. In Study 2, the psychometric properties of the new 12-item scale were tested in an independent sample of 11-year olds (N= 258), by examining its associations with related constructs of behavioural inhibition and activation, temperament. In study 3, the test-retest reliability of the 12-item scale was examined in a different sample of 10-year old children (N= 155). The psychometric properties of the 12-item scale were examined in a large sample of 17-years old adolescents (N= 1,174).

2.2 Methods & Results

The aims of the current chapter are examined in four studies across four independent samples. Details on the methods, analysis and results are presented separately for each study.

2.2.1 Study 1

2.2.1.1 Study 1: Methods

The main objective of Study 1 was to create a short and psychometrically robust Highly Sensitive Child (HSC) scale drawing on 38 existing sensitivity items for children, which have been adapted from the 27 items included in the adult HSP scale. Besides being brief and psychometrically sound, the self-report measure should be suitable for children and adolescents and reflect the same factor structure as the adult version. Once the HSC scale was created, it was then tested for its psychometric properties as well as for its associations with related constructs of behavioural inhibition and activation, temperament, and affect.

Sample: The sample included 334 children (251 girls and 83 boys) with a mean age of 12.06 years (range = 11-14 years; *SD* = 0.67) recruited from two secondary schools in East London, United Kingdom (one of the school was a girls-only school which explains the higher proportion of girls in this particular sample). The sample was ethnically diverse with 55.4% of Asian, 15.9% of African/Caribbean, 8.1% of White/European, 2.1% of Middle Eastern, and 18.6% of mixed ethnicity.

Procedures: Children were asked to complete all questionnaires on a computer at school during class. In order to create a short and psychometrically robust HSC scale that is comparable in content and structure to the adult scale, the factor structure of the adult scale was consulted (see **Appendix 2.1** for the HSP adult scale). As reported by Smolewska et al. (2006) a three factor structure seemed to fit the data collected with the adult HSP scale best, with 12 items loading on the factor "ease of excitation", 7 items on "aesthetic sensitivity", and 6 items on "low sensory threshold" (two items did not load clearly on any of the three factors and were excluded). In order to create a HSC scale that is comparable to the HSP scale, we first selected among the remaining 25 HSP items from Smolewska et al. (2006) factor analysis, those that had a factor loading of $> .5$ and could be easily adjusted for the use with children. Twelve items met these criteria. Then, a principal component analysis (PCA) was conducted, constrained to

three components (given that the HSP scale reflects three factors) across a pool of 38 sensitivity items for children (HSC-38, provided in **Appendix 2.2**). This was done to test whether the HSC-38 items would reflect similar factor loadings as those adult HSP items with the highest factor loadings for each of the three factors as reported by (Smolewska et al., 2006). The final 12-item HSC scale included 5 Ease of Excitation items, 4 Aesthetic Sensitivity items, and 3 Low Sensory Threshold items (see **Table 2.1** for a list of the specific items).

Measures: Children completed 38 items from an unpublished sensitivity scale (HSC-38, see **Appendix 2.2**) which has been developed initially to measure sensory-processing sensitivity in Dutch school-aged children (Walda, 2007). The 38 items aim at capturing the same information as the adult HSP scale (Aron & Aron, 1997). Items such as "*When someone is sad, that makes me feel sad too*", "*I find it unpleasant to have a lot going on at once*", and "*When I am hungry, I get in a bad mood*" were rated by children on a scale from 1 = "not at all", to 7 = "extremely", with higher scores indicating higher levels of sensitivity. The internal reliability of the 38 items was good with Cronbach's α = .92.

Behavioural inhibition and activation was measured with the 24-item Behavioural Inhibition and Behavioural Activation scales (BIS-BAS; Carver & White, 1994). The Behavioural Inhibition scale (BIS) is based on 7 items (e.g. "*Criticism or scolding hurts me quite a bit*", *"I worry about making mistakes"*) whereas the Behavioural Activation scale (BAS) features three subscales (i.e. "Reward Responsiveness", "Drive", and "Fun Seeking"). For the current study, all 17 BAS items (e.g. *"It would excite me to win a contest", "I'm always willing to try something new if I think it will be fun"*) were pooled into one scale. BIS-BAS items are rated on a Likert scale ranging from 1 = "very false" to 4 = "very true". Higher scores indicate higher levels of behavioural inhibition (BIS) and activation (BAS). In the current sample the internal reliability of BIS and BAS were α = .80 and α = .91, respectively.

Temperament was measured with the 65-item Early Adolescent Temperament Questionnaire-Revised (EATQR; Capaldi & Rothbart, 1992) which assesses 12 aspects of temperament (i.e. activation control, affiliation, attention, fear, frustration, high-intensity pleasure, inhibitory control, perceptual sensitivity, pleasure sensitivity, depressive moods, aggression, and shyness). Items (e.g. *"I feel shy about meeting new people", "I feel pretty happy most of the day", "When I am angry, I throw or break things")* are rated on a 5-point Likert scale, ranging from 1 = "almost always untrue of

you", to 5 = "almost always true of you". For the current study, we combined these subscales—as recommended by others (Putnam, Ellis, & Rothbart, 2001; Snyder et al., 2015)—into three superordinate dimensions of temperament: (a) effortful control (EC; based on attention, activation control, and inhibitory control), (b) negative emotionality (NE; based on fear, frustration and shyness), and (c) positive emotionality (PE; based on surgency, pleasure sensitivity, perceptual sensitivity and affiliation). Higher scores on each subscale indicate higher levels on that temperament dimension. The internal consistency of the scales were acceptable with α = .86 for EC, α = .69 for NE, and α = .84 for PE.

Positive and negative affect were measured with the child version of the Positive and Negative Affect scales (PANAS; Laurent et al., 1999). The Positive Affect (PA) scale includes 12 items (e.g. *"Interested", "Excited")* and the Negative Affect (NA) scale 15 items (e.g. *"Upset", "Guilty").* All items are rated on Likert scale, ranging from 1 = "not at all" to 5 = "almost every day". Higher scores indicate higher state levels of positive or negative affect. The internal consistency of the PANAS was good with α = .92 for PA and α = .93 for NA.

Data analysis: In order to create the HSC scale, principal component analyses (PCA) were conducted on the 38 sensitivity items (applying Varimax rotation with Kaiser normalization). For the first PCA the number of components was defined by Eigen values >.1, and in a second analysis the model was constrained to three components, informed by the 3-factor structure of the adult HSP scale (Smolewska et al., 2006). Twelve items were then selected out of the 38 items, that were most similar to the highest loading items of the adult HSP scale as reported by Smolewska et al. (2006). The PCA was then repeated with the 12 selected items in order to verify whether items would load on the specific component they had been selected for. Next, confirmatory factor analyses (CFA) were applied to the 12-item scale in order to test two competitive models (see **Figure 2.1** for an illustration of the difference between the two models): (a) a 3-factor model with five items in factor 1 (ease of excitation), four items in factor 2 (aesthetic sensitivity) and three items in factor 3 (low sensory threshold); and (b) a bi-factor model which includes a shared general factor in addition to the three separate factors, based on recent findings which suggest that the adult HSP scale fits a bi-factor model better than a 3-factor model (Lionetti et al., 2018). In order to test the bi-factor model, one of the factor loadings in the general factor and one of the loadings in each of the domain specific factors were set to 1 (Chen, West, & Sousa, 2006). The robust

maximum likelihood was used as estimation method. Two relative fit indices were considered for the evaluation of goodness of fit for each model: the Tucker Lewis index (TLI) and the comparative fit index (CFI), both of which perform well with small and large samples (the χ^2 statistic is extremely sensitive to sample size and not well suited for the current analysis). CFI and TLI values of > .95 and > .97, respectively, were considered as acceptable and good fit (Schermelleh-Engel, Moosbrugger, & Müller, 2003). The root mean square error of approximation (RMSEA) and the standardized root mean square residuals (SRMR) were also used. For RMSEA, values < .05 were considered as a good fit and values ranging from .05 and .08 as an adequate fit. For SRMR, values less than .08 were considered to reflect good fit (Schermelleh-Engel et al., 2003). The 3-factor and bi-factor models were compared according to three criteria: (a) qualitative evaluation of the fit indices of each model; (b) the CFI criterion according to which the null hypothesis of no differences between the two competing models should not be rejected if the difference in the CFIs between two nested models is smaller than |0.01| (Cheung & Rensvold, 2002); and (c) the scaled χ^2 difference test according to which the null hypothesis (i.e. no differences between the two competing models) should not be rejected if the associated *p* value is greater than .05 (Satorra, 2000) with lower χ^2 reflecting better model fit.

Internal reliability of the HSC scale was measured with Cronbach's α. A one-way ANOVA was conducted to test for ethnic differences in HSC and an independent samples t-test to investigate gender differences. The bivariate correlations were then tested between the mean of the 38 child sensitivity items, the mean of the newly created 12-item HSC scale and its subscales, as well as behavioural inhibition and activation, temperament, and affect. Furthermore, multivariate regression models were run to investigate convergent validity and to estimate how much of the variance in HSC was explained by related measures, including all HSC scales simultaneously as dependent variables in the same model and thus taking the interdependence among variables into account. Finally, divergent validity of the HSC scale was tested with the heterotrait-monotrait (HTMT) ratio of correlations (Henseler, Ringle, & Sarstedt, 2015). The HTMT ratio represents the average of the correlations of items across different constructs (e.g. HSC, BIS, PA etc.) relative to the average of the correlations of items within the same construct (e.g. the 12 HSC items). HTMT ratio values that are equal or lower than .85 indicate that divergent validity is met.

The level of significance for all analyses was set at $\alpha = .05$. Analyses were conducted using R software and related packages (Rosseels, 2016; semTools Contributors, 2016). All other analyses were conducted with SPSS version 20 (IBMCorp., 2011).

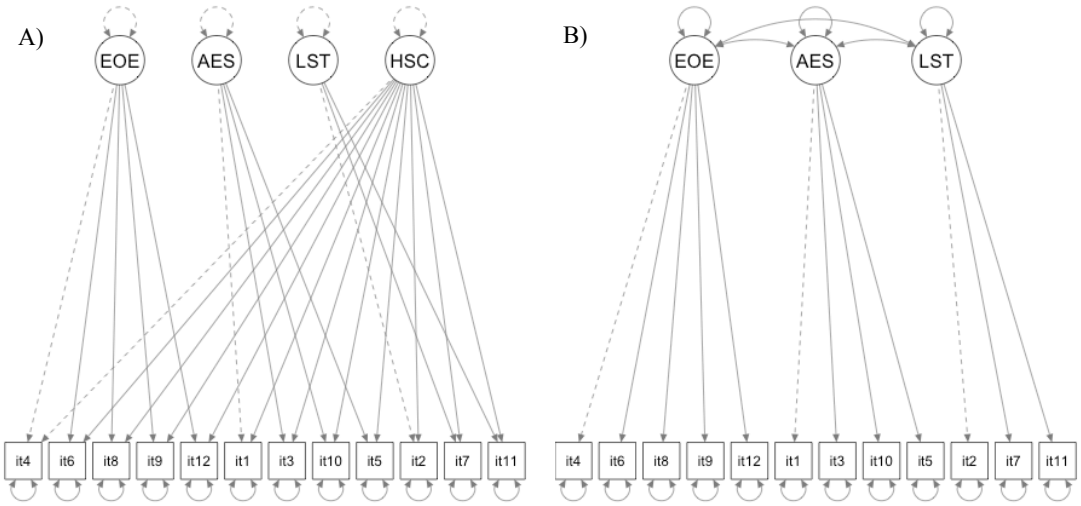


Figure 2.1 Graphical illustration of two competitive factorial models of HSC and subscales.
A) 3-factor model: EOE, LST and AES factors; B) bi-factor model: EOE, LST and AES factors plus a HSC general factor

2.2.1.2 Study 1: Results

Principal component and confirmatory factor analyses: Principal component analysis (PCA) of the HSC-38 resulted in nine principal components that accounted for 61% of the cumulative variance. However, the scree plot pointed towards a three-component solution. After constraining the PCA to three principal components, 40% of the variance was explained (see **Appendix 2.3** for detailed results). PCA of the 12 selected items suggested that the three principal components explained 55% of the cumulative variance. **Table 2.1** shows the 12 selected items and their loadings on the three principal components, reflecting the same three factors as reported with the adult HSP scale (Smolewska et al., 2006). The confirmatory factor analysis (CFA) of the 3-factor model showed acceptable model fit with $\chi^2 = 106.84$, $df = 51$, $p <. 001$; RMSEA= .06, 90% [C.I = .05, .08]; CFI/TLI = .907/ .880; SRMR = .06. Similar model fit indices emerged for the bi-factor model ($\chi^2 = 94.804$, $df = 46$, $p < .001$; RMSEA = .06, 90%, CIs [.05, .08]; CFI/TLI = .919/ .884 SRMR = .06). However, although the two models showed comparable fit indices the CFI difference (CFI [DIFF] = .012) and the scaled χ^2 difference (χ^2 [DIFF] = 11.8, $df = 5$, $p = .04$) between them suggests that the bi-factor model is the better fitting solution (more details of the CFA are provided in the **Appendix 2.4**).

Table 2.1 HSC rotated component matrix

Items		Factor 1 (EOE)	2 (AES)	3 (LST)
1	I find it unpleasant to have a lot going on at once	**.53**	.07	.15
2	Some music can make me really happy	.04	**.79**	-.02
3	I love nice tastes	.18	**.83**	.00
4	Loud noises make me feel uncomfortable	.35	.02	**.67**
5	I am annoyed when people try to get me to do too many things at once	**.71**	.26	-.02
6	I notice it when small things have changed in my environment	.29	**.44**	.03
7	I get nervous when I have to do a lot in little time	**.66**	.26	.23
8	I love nice smells	.13	**.79**	.24
9	I don't like watching TV programs that have a lot of violence in them	.05	.04	**.66**
10	I don't like loud noises	.10	.06	**.86**
11	I don't like it when things change in my life	**.48**	.22	.45
12	When someone observes me, I get nervous. This makes me perform worse than normal	**.70**	.00	.14

EOE= Ease of Excitation; AES=Aesthetic Sensitivity; LST=Low Sensory Threshold

Descriptive statistics and internal reliability. The mean values and standard deviations for the mean of the 38 child sensitivity items (HSC-38), the HSC total scale, the three HSC factors (Ease of Excitation, Aesthetic Sensitivity, and Low Sensory Threshold), and all other measures used in this study are shown in **Table 2.2**. The HSC scale showed adequate internal consistency with α = .79, 90% CIs [.75, .82]. HSC subscales showed acceptable but lower internal consistency which was to be expected considering the low item numbers in each subscale with α = .71, CIs [.65, .76] for Ease of Excitation, α = .73, CIs [67-78] for Aesthetic Sensitivity, and α = .66, CIs [.58, .72] for Low Sensory Threshold. There were no significant differences in HSC as a function of ethnicity ($F_{(51)} = 1.21$, $p = .45$). A small gender difference was observed, with females ($M = 4.41$, $SD = .93$) scoring significantly higher than males ($M = 4.07$, $SD = 1.08$) with $t_{(283)} = -2.55$, $p < .05$.

Table 2.2 Means and standard deviations of all measures (Study 1, 2, 3 and 4)

	Study 1	Study 2	Study 3		Study 4
			Session 1	Session 2	
HSC-38	4.15 (.90)	-	-	-	-
HSC	4.33 (.98)	4.68 (.93)	4.01 (.86)	4.04 (.84)	3.98 (.96)
HSC-EOE	4.13 (1.18)	4.59 (1.21)	3.70 (1.26)	3.67 (1.14)	3.81 (1.37)
HSC-AES	5.15 (1.23)	5.56 (1.08)	5.15 (1.02)	5.23 (0.91)	5.16 (1.00)
HSC-LST	3.58 (1.53)	3.67 (1.68)	3.01 (1.32)	3.10 (1.29)	2.70 (1.38)
BIS	18.88 (4.04)	19.66 (3.58)	-	-	-
BAS	37.36 (7.51)	39.11 (6.68)	-	-	-
EC	3.14 (.60)	3.30 (.57)	-	-	-
NE	3.00 (.58)	3.06 (.62)	-	-	-
PE	3.09 (.54)	3.26 (.52)	-	-	-
PA	44.54 (9.95)	-	-	-	-
NA	27.70 (10.7)	-	-	-	-
Neuro	-	-	-	-	15.97 (4.37)
Extra	-	-	-	-	21.75 (3.92)
Open	-	-	-	-	21.70 (3.66)
Agree	-	-	-	-	21.94 (3.52)
Cons	-	-	-	-	22.41 (3.65)

HSC-38 = Mean of 38 Highly Sensitive Child items; HSC = HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensory Threshold; BIS = behavioural inhibition system; BAS = behavioural activation system; EC = effortful control; NE = negative emotionality; PE = positive emotionality; PA = Positive Affect; NA = Negative Affect; Neuro= neuroticism; Extra=extraversion; Open= openness; Agree=agreeableness; Cons=conscientiousness

Bivariate correlations. Bivariate associations between all variables are reported in **Table 2.3**. Most importantly, the mean of the12-item HSC scale is highly correlated with the mean of the 38 child HSP items (r = .93). BIS and BAS are correlated with HSC and the three subscales except for Low Sensory Threshold, which was not associated with BAS. Regarding temperament, effortful control, negative and positive emotionality were correlated with HSC and all subscales except for Low Sensory Threshold, which was not correlated with Positive Emotionality. Finally, positive affect was positively correlated with Aesthetic Sensitivity (r = .41) and negative affect with Ease of Excitation (r = .16) and Low Sensory Threshold (r = .13).

Table 2.3 Bivariate correlations (Study 1)

		1	2	3	4	5	6	7	8	9	10	11	12	13
1	HSC-38	—												
2	HSC	**.93****	—											
3	HSC-EOE	**.80****	**.86****	—										
4	HSC-AES	**.68****	**.71****	**.43****	—									
5	HSC-LST	**.63****	**.69****	**.44****	**.18****	—								
6	BAS	**.42****	**.41****	**.31****	**.50****	.11	—							
7	BIS	**.55****	**.55****	**.49****	**.38****	**.36****	**.62****	—						
8	PE	**.29****	**.27****	**.17****	**.37****	.08	**.40****	**.32****	—					
9	NE	**.38****	**.37****	**.36****	**.19****	**.26****	**.21****	**.40****	**.61****	—				
10	EC	**.29****	**.27****	**.18****	**.29****	**.15***	**.39****	**.33****	**.82****	.**71****	—			
11	PA	**.16****	**.14***	-.01	**.41****	-.06	**.38****	**.14***	**.34****	.08	**.33****	—		
12	NA	**.15***	.09	**.16****	-.09	**.13***	-.08	.10	.04	**.19****	-.02	**-.38****	—	
13	Age	-.10	-.10	-.04	**-.17****	-.02	**-.18****	**-.19****	**-.18****	**-.12***	**-.21****	**-.15****	**.30****	—
14	Gender	**.18****	**.15***	.10	.10	**.15***	.06	**.19****	.09	**.13***	.10	-.08	.08	-.01

HSC-38 = Mean of 38 Highly Sensitive Child Items; HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensory Threshold; BIS = Behavioural Inhibition System; BAS = Behavioural Activation System; EC = Effortful Control; NE = Negative Emotionality; PE = Positive Emotionality; PA = Positive Affect; NA = Negative Affect; Gender: 1=male, 2=female; * $p < .05$; ** $p < .01$.

Multivariate regression. The first model, which included BIS, BAS, EC, PE, NE, PA, and NA as predictor variables of HSC explained 34% of the variance. The second model with the three subscales as outcomes explained 30% of the variance of Ease of Excitation, 35% of Aesthetic Sensitivity, and 17% of Low Sensory Threshold. Standardized parameter estimates and associated *p*-values are reported in **Table 2.4**.

Table 2.4 Multivariate regression results (Study 1)

	HSC			HSC-EOE			HSC-AES			HSC-LST		
	β	z	*p*	*β*	z	*p*	*β*	z	*p*	*β*	z	*p*
BAS	.13	1.73	.08	.14	1.72	.09	**.26**	**3.56**	**<.01**	-.11	-1.29	.20
BIS	**.38**	**5.36**	**<.01**	**.33**	**4.31**	**< .01**	**.16**	**2.37**	**.02**	**.37**	**4.39**	**<.01**
PE	.01	.09	.93	-.06	-.57	.57	**.26**	**3.29**	**<.01**	-.187	-1.38	.17
NE	**.24**	**3.24**	**<.01**	**.34**	**4.19**	**< .01**	.01	.19	.85	.16	1.57	.12
EC	-.12	-1.20	.23	-.18	-1.76	.08	-.18	-1.89	.06	.12	.89	.38
PA	.10	1.53	.13	-.02	-.22	.83	**.28**	**3.86**	**<.01**	-.01	-.22	.83
NA	.09	1.64	.10	.10	1.52	.13	.04	.70	.48	.07	1.21	.23

HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensory Threshold; BIS = Behavioural Inhibition System; BAS = Behavioural Activation System; EC = Effortful Control; NE = Negative Emotionality; PE = Positive Emotionality. Two models were run, the first including the HSC total score as the only dependent variable and the second model with EOE, AES and LST simultaneously included as dependent variables.

Divergent validity. Heterotrait-monotrait (HTMT) ratio of correlations values for each pair of measures ranged from .14 for Ease of Excitation-PA to .67 for Ease of Excitation-BIS, suggesting that divergent validity was established. Furthermore, associations among the HSC total score and subscales Ease of Excitation, Low Sensory Threshold and Aesthetic Sensitivity were consistently higher than associations between HSC and other measures (See **Appendix 2.5** for detailed results)

2.2.2 Study 2

In order to replicate the findings of Study 1, the same psychometric properties and associations with temperament, behavioural inhibition and activation were investigated in an independent sample.

2.2.2.1 Study 2: Methods

Sample: The sample included 258 children (113 girls and 145 boys) from a secondary school in East London, United Kingdom. Children were on average 11.17 years old (range = 11-12 years, *SD* = .38) and were of ethnically diverse backgrounds: White (20.9%), African/Caribbean (20.2%), Asian (34.9%), Middle Eastern (4%) and mixed-ethnicity (23.3%).

Procedure and measures: Children completed all measures on a computer during regular class at school. In order to measure environmental sensitivity, the 12-item HSC was used rather than the 38 child sensitivity items. In addition, children also reported on behaviour inhibition and activation with the BIS-BAS (Carver & White, 1994) and on temperament with the EATQR (Capaldi & Rothbart, 1992). Measures were used exactly the same way as described in Study 1. However, positive and negative affect (PANAS) were not measured in this sample.

Data analysis: The same methods and statistical analyses were applied as described in detail in Study 1.

2.2.2.2 Study 2: Results

Confirmatory factor analysis. The confirmatory factor analysis on the 12 items showed good model fit for the 3-factor model (χ^2 = 63.019, df = 51, *p* = .12; RMSEA = .03, 90% CIs [.00, .05]; CFI/TLI = .968/.959; SRMR = .05). For the bi-factor model, the negative variance of one statistically non-significant Ease of Excitation item was fixed to 0 (Chen et al., 2006). The results of the bi-factor model were satisfactory: χ^2 = 48.73, df = 46, *p* = .48; RMSEA = .01, 90% CIs [.00, .04]; CFI/TLI = .995/.994; SRMR = .04. The 3-factor and bi-factor models showed comparable fit indices with slightly stronger support for the bi-factor model. The CFI difference was significant and equal to .027—confirmed by a significant scaled χ^2 difference (χ^2 [DIFF] = 13.1, df = 4, p = .01)—and, thus, supporting the use of both the HSC total score as well as the individual Ease of Excitation, Aesthetic Sensitivity and Low Sensory Threshold subscales (see **Appendix 2.6** for more details).

Descriptive statistics and internal reliability. The mean scores and standard deviations for HSC, the three HSC subscales and all other measures used in this sample are presented in **Table 2.2**. The HSC scale showed acceptable internal consistency with a Cronbach's α of .72, 90% CIs [.66, .77] while the HSC subscales had slightly lower internal consistencies with α = .66, 90% CIs [.59, .72] for Ease of Excitation, α = .62, 90% CIs [.54, .69] for Aesthetic Sensitivity, and α = .63, CIs [.54, .70] for Low Sensory Threshold. Consistent with Study 1 there were no significant differences in HSC as function of ethnicity ($F_{(48)}$ = 1.27, p = .13) but the gender difference was only marginally significant ($t_{(245)}$ = -1.93, p = .06).

Bivariate correlations. Similar to Study 1, all HSC scales were positively correlated with both BIS and BAS except for Low Sensory Threshold, which was not associated with BAS (see **Table 2.5**). The strongest associations with BIS/BAS emerged between Ease of Excitation and BIS, and between Aesthetic Sensitivity and the BAS (r = .29 and r = .35, respectively). Regarding temperament, effortful control, negative and positive emotionality were associated with all HSC scales. However, the correlation between Ease of Excitation and negative emotionality and between Aesthetic Sensitivity and Positive Emotionality stood out (r = .49 and r = .50, respectively).

Table 2.5 Bivariate correlations (Study 2)

		1	2	3	4	5	6	7	8	9	10
1	HSC	—									
2	EOE	**.83****	—								
3	AES	**.61****	**.32****	—							
4	LST	**.69****	**.37****	.11	—						
5	BAS	**.25****	**.23****	**.35****	-.01	—					
6	BIS	**.32****	**.29****	**.24****	**.15***	**.66****	—				
7	PE	**.41****	**.28****	**.50****	**.15***	**.59****	**.44****	—			
8	NE	**.50****	**.49****	**.25****	**.31****	**.37****	**.50****	**.39****	—		
9	EC	**.48****	**.40****	**.43****	**.23****	**.61****	**.55***	**.67****	**.59****	—	
10	Age	.09	.05	.10	.07	.03	.02	-.08	-.12	-.06	—
11	Gender	.12	.06	.02	**.19****	.10	.12	.10	**.22****	.05	.02

HSC = Highly Sensitive Child Scale; EOE = Ease of Excitation; AES = Aesthetic Sensitivity; LST = Low Sensitivity Threshold; BIS = Behavioural Inhibition System; BAS = Behavioural Activation System; EC = Effortful Control; NE = Negative Emotionality; PE = Positive Emotionality; Gender: 1=male, 2=female; * p < .05; ** p < .01.

Multivariate regression. The multivariate regression models included BIS, BAS, EC, PE and NE as predictor variables of HSC and subscales. The model predicting HSC explained 26% of the variance and the model predicting the subscales explained 26% of the variance of Ease of Excitation, 26% of Aesthetic Sensitivity, and 15% of Low Sensory Threshold (see **Table 2.6**).

Table 2.6 Multivariate regression results (Study 2)

	HSC			HSC-EOE			HSC-AES			HSC-LST		
	B	z	*p*	*β*	Z	*p*	*β*	z	*p*	*β*	Z	*p*
BAS	-.16	-1.94	.05	-.06	-.63	.53	.07	.84	.40	**-.34**	**-3.71**	**<.01**
BIS	.04	.48	.63	.02	.28	.78	-.07	-1.50	.29	.12	1.31	.19
PE	**.24**	**2.69**	**.01**	.05	.51	.61	**.40**	**5.24**	**<.01**	.13	1.28	.20
NE	**.30**	**4.08**	**<.01**	**.39**	**4.37**	**<.01**	-.03	-.41	.69	**.23**	**2.57**	**.01**
EC	.19	.08	.08	.14	1.21	.23	.15	1.42	.16	.14	1.15	.25

HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensitivity Threshold; BIS = Behavioural Inhibition System; BAS = Behavioural Activation System; EC = Effortful Control. Two models were run, the first including the HSC total score as the only dependent variable and the second model with EOE, AES and LST simultaneously included as dependent variables.

Divergent validity. HTMT values for each pair of constructs ranged from .12 for Low Sensory Threshold-BAS to .71 for Aesthetic Sensitivity-PE and, hence, confirm divergent validity. Associations between the HSC total score and its subscales were consistently higher than association with the other measures (see **Appendix 2.7** for more details).

2.2.3 Study 3

Study 3 aimed at investigating test-retest reliability of the created 12-item HSC measure in an independent child sample.

2.2.3.1 Study 3: Methods

Sample: Data for this study were obtained from the Pictures and Words Study (PAWS). PAWS is a longitudinal study of information processing and mood featuring a sample of 155 children (Brown et al., 2014). Data were collected across three data waves with children recruited from two primary schools in London. For the current study, only data from the 12-item HSC scale collected at the third wave of data collection were used. For the current study, data were collected during the third wave resulting in a sample of 104 children (59 girls and 45 boys) at age 9.82 years (range = 8-11 years, *SD* = .45). Eighty-one percent of the sample identified as white.

Procedure and measures: The third wave of data collection comprised of two data collection sessions scheduled to take place approximately two-three weeks apart (mean interval = 15 days, range 9-22 days, *SD* = 2.46). Children were seen individually in a quiet classroom and completed a computerised version of the HSC scale at both sessions (via EPrime 2.0) with responses made using the computer keyboard. Items were presented onscreen but also read aloud to ensure comprehension.

Data analysis: Internal reliability of the 12-item HSC scale was examined with Cronbach's α and test-retest reliability was calculated by correlating scores for HSC and the three subscales from Session 1 with scores of repeated measurement at Session 2. A test-retest reliability of .70 or higher was considered adequate (McCrae, Kurtz, Yamagata, & Terraciano, 2011).

2.2.3.2 Study 3: Results

Descriptive statistics and internal reliability. Mean scores and standard deviations for the HSC sum score and the three subscales are provided in **Table 2.2**, separately for each of the two data collection sessions. The HSC scale showed acceptable internal consistency with α = .71 and .74 for Session 1 and Session 2, respectively. The subscales showed lower internal consistency with α = .73/ .69 for Ease of Excitation, α = .49/ .46 for Aesthetic Sensitivity, and α = .49/ .55 for Low Sensory Threshold.

Test-retest reliability. Test-retest reliability estimates were acceptable, with HSC total score $r = .68$, and the subscales EOE: $r = .66$, AES= .57 and LST = .78, all with $p < .01$. Furthermore, estimates remained stable when the interval between data collection sessions was partialled out.

2.2.4 Study 4

In Study 4 the performance of the developed 12-item HSC scale was tested in a large sample of adolescents followed by exploring associations with the Big Five personality traits.

2.2.4.1 Study 4: Methods

Sample: The sample for the current study included a subset of adolescent twin pairs from the Twins Early Development Study (TEDS), a large longitudinal epidemiological study of over 16,000 twin pairs born in England and Wales from 1994 through 1996. TEDS includes extensive data on various aspects of development, including cognitive abilities, personality, behaviour, school and family environment, collected when the twins were aged 2, 3, 4, 7, 8, 9, 10, 12, 14, and 6 years of age. The sample is reported to be representative of the of the UK population (Kovas et al., 2007). Twins' zygosity has been determined via parental ratings of physical similarity, which is reported to be 95% accurate when compared to DNA analysis (Price et al., 2000), as well as DNA testing in instances where zygosity could not be determined based on physical similarity. More details on the TEDS sample are available from (Haworth, Davis, & Plomin, 2013). The data used in the current study were obtained during the planned wave of TEDS data collection, when twins were approximately 16 years old. Data on the 12-item HSC scale was collected for 2,945 twins. After excluding participants with severe medical disorders, history of perinatal complications, or unknown zygosity (n=77), the HSC sample consisted of 2,868 individuals. Data on the Big Five personality traits was available for a subset of the same sample (N=1,156). For the current study, only data from one sibling per twin pair was included (random selection) in order to account for relatedness between individuals in this particular sample. The final sample included 1,431 adolescents (595 males, 836 females) with HSC data and 579 individuals with Big Five personality data. Mean age of the sample was 17.06 (range = 15-19 years, SD = .88) on return of the HSC questionnaires. The ethnicity of the majority (93%) of the sample was identified as Caucasian.

Procedure and measures: Data for the measures used in the current chapter were obtained by self-report, via web-based questionnaires.

Environmental sensitivity was measured with the 12-item HSC scale.

Big Five personality traits of agreeableness, extraversion, neuroticism, openness to experiences and conscientiousness were measured with the 30 item Five Factor Model Rating Form (Mullins-Sweatt, Jamerson, Samuel, Olson, & Widiger, 2006). Items (e.g. *"fearful, apprehensive versus relaxed, unconcerned, cool", "strange, odd, peculiar, creative versus pragmatic, rigid.")* were rated on a Likert scale ranging from 1 = "low" to 5 = "high". Higher scores indicate higher levels of the personality trait. Internal reliability of the scale was acceptable with α = .73 for neuroticism, α = .70 for extraversion, α = .65 for openness, α = .65 for agreeableness, and α = .75 for conscientiousness.

Data analysis: The factor structure (confirmatory factor analysis) and internal reliability of the HSC scale were examined by applying the same methodological approaches as in Studies 1 and 2. Association between HSC, HSC subscales and the Big Five personality traits were investigated with bivariate correlations. Furthermore, multivariate regression and heterotrait-monotrait ratio of correlations analysis were applied to investigate divergent validity, following the same procedures adopted in Studies 1 and 2.

2.2.4.2 Study 4: Results

Confirmatory factor analysis. The 3-factor model (Ease of Excitation, Aesthetic Sensitivity, Low sensory threshold) yielded good model fit (χ^2 = 323.88, *df* = 51, *p* < .001; RMSEA = .06, 90% CIs [.06, .07], CFI/TLI = .935/.91; SRMR = .05). The bi-factor model also fit the data well (χ^2 = 286.53, *df* = 46, *p* < .001, RMSEA = .06, 90% CIs [.05, .07], CFI/TLI = 945/921, SRMR = .70). (See **Appendix 2.8** for CFA details). The two models showed comparable fit indices with slightly stronger support for the bi-factor model. The CFIs difference was trivial (equal to .01) though in the presence of a significant scaled χ^2 difference (χ^2 [DIFF] = 47.2, *df* = 5, *p* < .001).

Descriptive statistics and internal reliability. Mean scores and standard deviations for HSC, the three HSC subscales, and the Big Five personality traits are presented in **Table 2.2**. Females (M = 4.13, SD = .96) scored significantly higher than males (M = 3.78, SD = .92) with $t_{(1429)} = 6.81$, $p < .001$. Internal consistency was good for the HSC total scale (α = .82) and acceptable for the subscales (Ease of Excitation with α = .81; Aesthetic Sensitivity with α = .65; Low sensory threshold with α = .71).

Bivariate correlations. Unadjusted associations between HSC and the Big Five personality traits are presented in **Table 2.7**. HSC was positively associated with neuroticism (r = .31) and openness (r = .18) and negatively with extraversion (r = -.18) but did not correlate with agreeableness and conscientiousness. While Ease of Excitation and Low sensory threshold correlated with neuroticism (r = .38, and r = .22, respectively) and extraversion (r = -.28 and r = -.22, respectively), Aesthetic Sensitivity was not associated with neuroticism but correlated positively with extraversion (r = .20), openness (r = .25), and conscientiousness (r = .16).

Table 2.7 Bivariate correlations (Study 4)

	1	2	3	4	5	6	7	8	9	10
1 HSC	—									
2 HSC-EOE	**.89****	—								
3 HSC-AES	**.58****	**.29****	—							
4 HSC-LST	**.74****	**.54****	**.18****	—						
5 Neuroticism	**.31****	**.38****	-.00	**.22****	—					
6 Extraversion	**-.18****	**-.27****	**.20****	**-.22****	**-.36****	—				
7 Openness	**.18****	.05	**.25****	**.17****	-.05	**.27****	—			
8 Agreeableness	.03	-.03	.04	.08	**-.21****	**.19****	**.25****	—		
9 Conscientious	-.01	**-.13****	**.16****	.03	**-.19***	**.29****	**.09***	**.26****	—	
10 Age	.02	**.01**	**.07****	-.01	**-.01***	.05	.04	.04	-.02	—
11 Gender	**-.18****	**-.15****	**-.07****	**-.18****	**-.22****	.04	-.08	**-.12****	-.08	-.03

HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensitivity Threshold; Gender: 1=male, 2=female; * $p < .05$; ** $p < .01$.

Multivariate regression. The multivariate regression model with the five personality traits as predictor variables explained 14% of the variance of HSC. A second model with the HSC subscales as outcome variables explained 17% of the variance of Ease of Excitation, 10% of Aesthetic Sensitivity, and 14% of Low sensory threshold (See **Table 2.8** for the standardized parameter estimates).

Table 2.8 Multivariate regression results (Study 4)

	HSC			HSC-EOE			HSC-AES			HSC-LST		
	β	z	*p*	*β*	Z	*p*	*β*	z	*p*	*β*	Z	*p*
N	**.28**	**6.39**	**<.01**	**.31**	**6.83**	**<.01**	.07	1.44	.15	**.18**	**3.88**	**<.01**
E	**-.15**	**-3.33**	**<.01**	**-.17**	**-3.86**	**<.01**	**.14**	**2.96**	**<.01**	**-.25**	**-5.29**	**<.01**
O	**.19**	**4.31**	**<.01**	.07	1.45	.15	**.22**	**4.62**	**<.01**	**.21**	**5.21**	**<.01**
A	.04	.87	.39	.05	1.11	.27	-.06	-1.26	.21	.07	1.70	.09
C	.04	1.03	.30	-.06	-1.34	.18	**.12**	**2.77**	**<.01**	.10	2.33	.02

N= neuroticism; E=extraversion; O=openness; A=agreeableness; C=conscientiousness; HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensitivity Threshold. Two models were run, the first including the HSC total score as the only dependent variable and the second model with EOE, AES, and LST simultaneously included as dependent variables.

Divergent validity. HTMT values ranged from .12 for Low sensory threshold–Conscientiousness to .48 for Ease of Excitation-Neuroticism providing evidence of divergent validity. Similar to the previous studies reported in this paper, associations among the HSC total score and subscales Ease of Excitation, Low sensory threshold and Aesthetic Sensitivity were consistently higher than associations with other measures (see **Appendix 2.9** for more details).

2.3 Discussion

As detailed in **Chapter 1**, the highly sensitive personality trait has been suggested to reflect a phenotype of environmental sensitivity in differential susceptibility theories (Pluess, 2015). The original measure however, has been validated for use in adult populations only. The main aim of this study was to develop and validate a brief measure of highly sensitive personality for use with children and adolescents, based on the adult version. The development and psychometric properties of the new scale were conducted via 4 studies. Overall, the newly developed scale showed comparable factor structure, internal reliability and convergent and divergent validity, to the adult version. The results form each study are discussed separately in the following sections.

Study 1. The aim of Study 1 was to develop a brief measure of highly sensitive personality that reflects the adult HSP scale according to the three factors reported by Smolewska et al. (2006). The PCA and factor analysis identified 12 items from a pool of 38 items to reflect the same 3-factor structure as the adult scale. Importantly, the confirmatory factor analyses suggested that although the measure consists of three distinct subscales, these subscales also load on a general factor of sensitivity. Hence, the total score of the scale reflects general sensitivity to environmental influences and the three subscales reflects specific aspects of environmental sensitivity. Specifically, the significant correlations between AES and the behavioural activation system (BAS) and positive emotionality and affect seem to reflect the Aesthetic Sensitivity factor's propensity for sensitivity to positive aspects of the environment, whereas Ease of Excitation and Low sensory threshold tend to reflect sensitivity to more negative contextual factors, as evident by their correlations with the behavioural inhibition system (BIS) as well as negative emotionality and negative affect. This may also explain why the total score was associated with both negative *and* positive emotionality. Finally, the results of multivariate regression analyses and heterotrait-monotrait ratio of correlations analysis established the divergent validity of the measure, indicating that environmental sensitivity as measured with the HSC scale does not simply reflect well-known temperament traits and affect.

Study 2. The findings of Study 2 further supported the findings from Study 1 in an independent sample. Factor analysis results confirmed that the total HSC score captures general environmental sensitivity, while the 3 subscales reflect different aspects of sensitivity. In addition, while the total score was associated with both positive and negative affect, the bivariate correlations provided further suggestive evidence that

Aesthetic Sensitivity may reflect sensitivity to more positive environmental aspects, whereas Ease of Excitation and Low sensory threshold seem to capture sensitivity to more negative contextual factors. The regression results with temperament traits as predictors of HSC failed to account for the majority of the variance of HSC, and heterotrait-monotrait ratio of correlations findings suggested that environmental sensitivity is not fully explained or captured by existing concepts.

Study 3. The aim of Study 3 was to examine the test-retest reliability of the HSC scale. The results suggested that the test-retest reliability of the HSC scale was acceptable in a sample of 8-11 year old children. Although there was substantial stability across measurements, mean scores did show some variability over time. This suggests that the measure may pick up measurement error or short-term changes in self-reported sensitivity. It is possible that the reliability of the scale is affected by the younger age of this sample, and might be higher at older ages; though this remains to be tested.

Study 4. The aim of Study 4 was to test the newly developed scale in an adolescent sample, and examine its relationship with personality traits. Similar results were found in this sample, with factor analyses identifying 3 factors, but also that a bi-factorial model fit the data best. This confirmed that the total score reflects general sensitivity, with three distinct sensitivity components. Bivariate correlations provided additional evidence that the subscales capture different aspects of sensitivity with Aesthetic Sensitivity reflecting openness and to a lesser degree conscientiousness. Ease of Excitation and Low sensory threshold were found to be associated with higher neuroticism and lower extraversion. The results of regression analysis with the Big Five personality traits as predictors of sensitivity and heterotrait-monotrait ratio of correlations confirmed divergent validity of HSC, with personality traits explaining only 14% of the variance in HSC.

2.3.1 General discussion

Overall, the results from these studies suggest that the newly developed measure of environmental sensitivity for children and adolescents reflects the adult version as developed by Aron and Aron (1997), and confirmed the same factor structure as reported in other studies on this trait (e.g. Smolewska et al., 2006). In addition, observed associations with temperament and personality traits provide more insight into the three identified factors of the scale. Whereas Ease of Excitation and Low sensory threshold seem to be more strongly associated with traits that reflect sensitivity to negative

environmental factors (e.g. BIS, negative emotionality, negative affect, and neuroticism), Aesthetic Sensitivity correlated with measures that reflect sensitivity to more positive experiences (e.g. BAS, positive emotionality, extraversion, openness, conscientiousness). The observed correlations between the total score and both BIS and BAS as well as both negative and positive emotionality suggests that this phenotype encompasses sensitivity to both positive and negative influences, consistent with the differential susceptibility theories. Specifically, and as reviewed in **Chapter 1,** while vantage sensitivity (Pluess, 2017; Pluess & Belsky, 2013b) refers to individual differences in sensitivity to positive environmental influences, and diathesis-stress (Monroe & Simons, 1991) refers to inter-individual variability in sensitivity to negative environmental influences, differential susceptibility theories (Belsky, 1997a, 2005; Belsky, Bakermans-Kranenburg, et al., 2007; Belsky & Pluess, 2009, 2013a; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011) suggest that sensitive individuals are more affected by both negative as well as positive environmental influences. Examining the findings in light of these theoretical models the total score of the scale may capture general sensitivity as described in the differential susceptibility theories model, while the Ease of Excitation and Low sensory threshold subscales reflect *diathesis-stress* and Aesthetic Sensitivity subscale reflect *vantage sensitivity*. Although this interpretation may seem plausible in light of the discussed theoretical models and observed empirical findings, further research is required to empirically validate if these subscales do moderate the outcomes of environmental influences in the suggested ways. In the absence of such empirical confirmation, caution is warranted when trying to use the subscales as distinct aspects of sensitivity to positive and negative environmental influences, given that the original scale was not developed with having separate subscales in mind (Aron & Aron, 1997).

2.3.2 Strengths and limitations

The main strengths of the current chapter on the development of a new measure of environmental sensitivity for children and adolescents were the availability of 4 large samples which enabled replication of results as well the application of sophisticated statistical procedures. However, findings should be considered in light of methodological limitations. First, all studies used here are based on self-report, and the scale was not examined for its association with other more objective measures of environmental sensitivity. Second, all data were provided by children and adolescents residing in the United Kingdom. Although some of the included samples were highly

diverse, the results require replication across other populations to test whether similar findings would emerge in other populations. Finally, although the HSC scale has been designed to reflect the same factor structure as the adult HSP scale, measurement invariance between child and adult samples has not been established yet.

2.3.3 Future studies

Future research should continue to investigate the hypothesised moderating function of environmental sensitivity regarding the effects of various environmental factors (e.g. parenting quality, education etc.) and psychological intervention. This provides a more stringent test of whether this newly developed brief measure appropriately captures environmental sensitivity, including whether and how its three components interact with environmental influences to moderate outcomes. In addition, future studies could aim to develop other non-questionnaire based measures of environmental sensitivity, as well as developing measures to assess sensitivity at even younger ages. Future work should also aim at identifying the specific psychological and biological mechanisms underlying individual differences in environmental sensitivity, including neuroimaging studies, as well as molecular genetics studies. Considering the observed associations with personality traits and temperament, future research should also explore the shared aetiology of environmental sensitivity with these traits. Finally, since environmental sensitivity has been developed based on a western cultural concept of sensitivity, future studies could investigate the validity of this measure and its application across other cultures.

2.3.4 Conclusions

The newly developed measure of the Highly Sensitive Child scale is a psychometrically valid measure for use in children and adolescents that is able to characterise environmental sensitivity in these developmental stages. While environmental sensitivity as measured by this scale is related in meaningful ways to other temperament and personality traits as proposed by the sensory processing sensitivity theory (Aron & Aron, 1997), it is distinct from them. Furthermore, recent studies using the newly developed HSC scale further validate this measure of environmental sensitivity, by providing empirical evidence that HSC moderates the outcomes of environmental influences in response to a wide range of environmental influences, consistent with the differential susceptibility interaction pattern (e.g. Donley, Fine, Simmons, Pluess, &

Cauffman, submitted; Nocentini et al., 2018; Pluess & Boniwell, 2015; Slagt et al., 2018).

Chapter 3

Heritability of environmental sensitivity and its genetic overlap with personality, depression, and anxiety

3.1 Introduction

As presented in **Chapter 1**, differential susceptibility theories (i.e. sensory processing sensitivity: Aron & Aron, 1997; differential susceptibility hypothesis: Belsky & Pluess, 2009; biological sensitvity to context: Boyce & Ellis, 2005) suggest that there exist individual differences in general sensitivity to environmental influences, with some individuals more sensitive to the effects of both negative and positive environmental influences. Whilst the three prominent differential susceptibility theories differ in the hypothesised mechanisms underlying this variation (see **Chapter 1, Section 1.1.3**), and regarding what characteristics may best reflect environmental sensitivity (e.g. genetic variation, infant temperament, physiological processes, personality, etc.), they all converge on the proposition that genetic factors play a significant role (Aron & Aron, 1997; Belsky & Pluess, 2009; Boyce & Ellis, 2005). However, no studies to date have examined the heritability of environmental sensitivity in order to empirically test the proposed contribution of genetic influences to variations in sensitivity. The main aim of this chapter is therefore to estimate, for the first time, the heritability of environmental sensitivity as measured by the Highly Sensitive Child scale, developed in the previous chapter. The second aim of this chapter was to examine the genetic architecture of environmental sensitivity, informed by the findings on its factor structure and associations with other traits. Specifically, this chapter examines the genetics of environmental sensitivity as a function of its three underlying factors, as well as its overlap with the Big Five personality traits, anxiety and depression.

Growing evidence supports the hypothesis of differential susceptibility theories that heightened environmental sensitivity increases reactivity/responsivity to both negative and positive environmental influences (see **Chapter 1**, **Section 1.2** for a review). Specifically, heightened environmental sensitivity is proposed to influence the impact of environmental influences in a "*for better and for worse*" manner, with more sensitive individuals being more negatively affected by adverse experiences (e.g. stressful life events) but also benefiting more from the nurturing aspects of positive environmental influences (e.g. psychological interventions) (Belsky, Bakermans-Kranenburg, et al., 2007). The evidence base includes studies featuring different markers of environmental sensitivity, including children's difficult temperament (e.g. Pluess & Belsky, 2008), genetic variants (e.g. Hankin et al., 2011), physiological reactivity (e.g. Obradovic et al., 2010) and highly sensitive personality trait (e.g. Acevedo et al., 2017) all showing that these markers moderate the impact of a wide range of environmental influences

consistent with a "*for better and for worse*" interaction pattern. Evidence in support of the genetic basis of environmental sensitivity is predominately drawn from gene by environment interaction (GxE) studies. Such studies typically test whether specific genetic variants (e.g. *5-HTTLPR*) interact with environmental risk factors (e.g. childhood maltreatment) in the prediction of an outcome (e.g. depression). Comprehensive reviews of GxE literature by Belsky and Pluess (2009, 2013a), and subsequent research using the differential susceptibility framework, have identified a number of genetic variants as markers of environmental sensitivity (see **Chapter 4**, **Section 4.1.2.2**). For example, the short allele of the *5-HTTLPR* and the *DRD4* 7-repeat allele have been consistently found to influence psychological outcomes not only "for worse", in response to adversity, but also "for better", at the positive 'end' of the environmental quality spectrum (For meta-analysis of studies with these variants, see: Bakermans-Kranenburg & van IJzendoorn, 2011; van IJzendoorn, M. H. et al., 2012). The *5-HTTLPR* short allele has, for instance, been found to moderate the impact of maternal responsiveness on children's moral development (Kochanska et al., 2011), the effect of child maltreatment on children's antisocial behavior (Cicchetti et al., 2012) and the benefit of supportive parenting on child positive affect (Hankin et al., 2011), both for better and for worse. There are, however, at least two caveats that have to be considered when interpreting research findings from GxE studies as evidence for the genetic basis of environmental sensitivity. First, such studies indicate that these genetic factors moderate the impact of the examined environmental influences on the measured outcomes, but they have not been tested for their direct associations with individual differences with phenotypic environmental sensitivity. Therefore, it is difficult to determine whether these genes are relevant for the aetiology of the environmental sensitivity phenotype, an empirical question that is the focus of **Chapter 4**. Second, even if we were to assume that these genetic factors are relevant for the aetiology of phenotypic environmental sensitivity, these GxE results do not provide an estimate of *how much* of the variability in environmental sensitivity might be explained by genetic influences. Examining the heritability of environmental sensitivity is therefore an important first step.

Heritability is commonly defined as the proportion of variance in a trait explained by genetic influences in a specific population, at a specific time. Genetic influences may be defined as the combined effect of all loci (additive effects), including possible allelic interactions within loci (dominance) and between loci (epistasis). Heritability estimates for a phenotype mainly include narrow-sense heritability, defined as $h^2 = V_A/V_P$, where

the estimate h^2 captures the proportion of phenotypic variation due to additive genetic effects only (V_A); or Broad-sense heritability, defined as $H^2 = V_G/V_P$, where the estimate captures the proportion of phenotypic variation due to genetic influences that may include dominance and epistasis effects, as well.

There are two main approaches in obtaining heritability estimates. The older, family-based approach takes the genetic relatedness between individuals in family, sibling, adoption or twin samples into account, and the heritability estimate is derived based on the ratio of variance components that include environmental or genetic effects (Plomin, DeFries, Knopik, & Neiderheiser, 2013). In twin designs, one of the most widely used methods (Polderman et al., 2015), the heritability of a trait is estimated by comparing the correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs. Briefly, it is assumed that, since the pre- and post-natal environments of MZ and DZ twin pairs are similar but MZ pairs share all and DZ pairs share approximately half of their genome, the higher similarity between MZ twin pairs on a trait can be attributed to their genetic similarity and implies genetic influences on the examined trait (see **Section 3.3.2** for more details on this approach). The more recent approaches, called SNP-based heritability, use molecular genetic data, typically from large samples of unrelated individuals, to estimate the heritability of a phenotype. For example, in the Genome-wide Complex Trait Analysis (GCTA) method (Yang, Lee, Goddard, & Visscher, 2011), this is done by obtaining the probability of genetic similarity between unrelated individuals and comparing this to their measured phenotypic similarity. (i.e. plotting prediction error against observed relatedness). If two unrelated individuals are genetically similar, and their measured phenotypes are also correlated, this indicates that those genes affect the phenotype.

While the SNP-based approaches allow estimation only of additive genetic effects (narrow sense heritability), and provide a more conservative/lower estimate of heritability, twin models can estimate heritability due to both additive and non-additive effects. However, twin models rely on certain assumptions, which may be violated, such as no gene-environment correlation or interactions, assortative (non-random) mating, twins being representative of the general population (i.e. singletons), and MZ twin pairs and DZ twin pairs sharing equally similar environments. Violation of the latter assumption (i.e. the equal Environments assumption or EEA) is considered to contribute to inflated heritability estimates (Fosse, Joseph, & Richardson, 2015). Multiple tests of this assumption have been carried out, for example, by testing whether MZ twins are

treated more similarly based on their physical similarity (Hettema, Neale, & Kendler, 1995). The results have generally not found a significant difference, suggesting that violations of EEA may not be as problematic as suggested, but nevertheless inflating heritability estimates by about 10% (Felson, 2014). Regardless of the limitations of both approaches, one advantage of twin designs is that the requirement for sufficiently powered sample sizes is more easily met (1000 vs. > 10,000 for GWAS approaches), sustaining their relevance as an important methodological tool in behavioural genetics.

Although twin designs are not able to provide information on the specific molecular genetic factors underlying the phenotype of interest, they can provide insight into the genetic architecture of it. The multivariate twin design approach, for example, is able to test whether and to what extent the correlation between two or more phenotypes is due to their correlating genetic influences. The insight into the genetic architecture of correlating phenotypes, via multivariate twin modeling, is valuable, especially if the genetic aetiology of one of the phenotypes is little-known. It is possible to use the knowledge of the molecular genetics of the better-known correlating phenotypes to advance understanding of the genetics of the lesser-known phenotype of interest.

As presented in **Chapter 2**, environmental sensitivity is associated with certain personality traits and outcomes, such as neuroticism, extraversion, depression and anxiety (e.g. Acevedo, Aron, Pospos, & Jessen, 2018; Aron & Aron, 1997; Hofmann & Bitran, 2007; Liss et al., 2008; Smolewska et al., 2006). Using multivariate twin models, it is possible to provide a first glimpse into the relationship between environmental sensitivity and these phenotypes. In addition, multivariate twin models can be used to provide further insight into the genetic architecture of environmental sensitivity, by determining the extent to which correlations between composite components of the psychometric measure are due to shared and distinct genetic/environmental influences. Specifically, as reported in **Chapter 2,** factor analysis of the HSC scale has identified three factors, each tapping into different aspects of environmental sensitivity; Low Sensory Threshold (LST) captures variations in the threshold for reactivity to sensory stimuli; Ease of Excitation (EOE) manifests in being easily overwhelmed by contextual emotional psychological stimuli; and Aesthetic Sensitivity (AES) is characterised by greater attention to contextual details and aesthetic appreciation. In addition, the results indicated that a bi-factorial solution was the best fitting model, so that whilst the component correlated to form a general factor, they retained specific variance. Importantly, it was found that AES may capture variations in

sensitivity to more positive aspects of the environment, while EOE and LST capture variations in sensitivity to more negative contexts. This was evidenced through a distinct pattern of associations between these factors and other traits. For example, whilst Ease of Excitation and Low Sensory Threshold were more strongly associated with behavioural inhibition, negative emotionality, negative affect and neuroticism; Aesthetic Sensitivity correlated more strongly with behavioural activation, positive emotionality, extraversion, openness and conscientiousness. Considering these findings, it is possible that the genetic influences underlying variations in environmental sensitivity reflect the factor structure of this phenotype. Thus, it is hypothesised that there will be evidence of genetic influences that are shared between the three components and represent variations in general levels of sensitivity, as well as genetic influences that are distinct to each component and reflect specific biological substrate underlying sensitivity to more positive or negative influences.

3.1.1 Aims

There were three main aims for this chapter. The first aim was to examine the heritability of environmental sensitivity, using the Highly Sensitive Child scale (Pluess et al., 2018), in a large sample of adolescent twins from the UK (*N*= 2,868), via twin modelling. There are no previous heritability estimates for this phenotype; however, it is thought to be moderately heritable, as a recent meta-analytic study of the heritability studies from the past 50 years indicates that most human traits are about 50% heritable (Polderman et al., 2015). The second aim was to examine the genetic architecture of environmental sensitivity as a function of its three identified factors, using a multivariate twin design. It is expected that the three factors of environmental sensitivity reflect a general factor, but that they also show distinct genetic/environmental influences underlying each component. The third aim was to further investigate the correlations between environmental sensitivity and the Big-Five personality traits and anxiety and depression, using a multivariate twin design. It was expected that the correlation between these phenotypes reflects shared genetic and/or environmental influences in their aetiology, though the extent to which these influences would be each implicated is unclear.

3.2 Methods

3.2.1 Sample and measures

Sample: The sample for the current study included a subset of twins from the Twins Early Development Study (TEDS); this is a large longitudinal epidemiological study of over 16,000 twin pairs born in England and Wales from 1994 through 1996, as detailed in **Chapter 2, Section 2.2.4.1**. Briefly, the data for the current study were obtained during the planned waves of TEDS data collection, when twins were approximately 16 years old. The sample for the current study included all individuals *(N*= 2,945) who completed the Highly Sensitive Child scale (Pluess et al., 2017). After excluding participants with severe medical disorders, a history of perinatal complications or unknown zygosity (*n*= 77), the final sample consisted of 2,868 individuals (Monozygotic twins (MZ) = 1,011; same-sex Dizygotic twins (DZ) = 901; opposite sex twins = 956). Depression and anxiety data were available for all 2,868 individuals. The Big Five personality data were available for a subset of the sample (*N*= 1,156), which included 445 MZ twins, 354 same sex DZ twins and 357 opposite sex twins. The mean age of the participants upon returning the Highly Sensitive Child questionnaires was 17.06 (*SD*= .88). Twins' zygosity in TEDS has been determined via parental ratings of physical similarity, which is reported to be 95% accurate when compared to DNA analysis (Price et al., 2000), as well as DNA testing in instances where zygosity could not be determined based on physical similarity. The ethnicity of the majority (93%) of the sample was self-reported as white European.

Measures:

Environmental sensitivity was measured with the 12-item self-report Highly Sensitive Child (HSC) scale by Pluess et al. (2018), as reported in detail in **Chapter 2**. The internal reliability of the measure in the current sample was good, with α = .81 for the main scale (HSC) and acceptable with α = .64, .81 and .70 for the AES, EOE and LST subscales, respectively.

Personality was measured using the Five Factor Model Rating Form (FFMRF), by Mullins-Sweatt et al. (2006). This measure contains short descriptors to define the personality traits of agreeableness, extraversion, neuroticism, openness to experience and conscientiousness. This is the same questionnaire used in **Chapter 2, Study 4.** The internal reliability of the scale in the current sample was in the acceptable range for each of the subscales of neuroticism (α = .71), extraversion (α = .72), openness (α = .63),

agreeableness (α = .69) and conscientiousness (α = .77).

Depression was measured via the Mood and Feelings Questionnaire (MFQ; Angold, Costello, Messer, & Pickles, 1995). The questionnaire includes 12 self-report items and has been developed to index children and adolescent's depressive symptoms (e.g. not feeling loved, feeling lonely, not enjoying anything). The items are rated on a Likert scale (0=not at all to 3=very true), with higher scores on the indicating higher levels of depressive symptoms. Questionnaires were sent to the participating families to be completed by children and returned by post. The internal reliability of the scale was α = .90.

Anxiety was measured via the Childhood Anxiety Sensitivity Index (CASI; Silverman, Fleisig, Rabian, & Peterson, 1991). This questionnaire comprises 18 self-report items indexing anxiety sensitivity (e.g. fear of the experience of anxiety, and the belief that anxiety has negative consequences). The items are rated on a Likert scale (0=not to 3=very true), higher scores on the scale indicating higher levels of anxiety sensitivity. The data for this measure were collected by sending the questionnaires to the participating families to be completed by children and returned by post. The internal reliability of the scale was α = .87.

3.2.2 Data analysis

Analytical approaches: Univariate and multivariate twin design approaches were used to examine the three aims of this chapter. Twin design takes advantage of our knowledge about the genetic relatedness of Monozygotic (MZ) and Dizygotic (DZ) twins to estimate the contribution of genetic and environmental factors to observed phenotypic variations in a trait. Falconer's Formula (Falconer & Mackay, 1998) has been used to arrive at estimates for the contribution of the genetic and environmental influences on a trait, using the interclass correlations between MZ and DZ twin pairs (Rijsdijk & Sham, 2002). This is done by typically partitioning the total phenotypic variance (V) of a trait into additive genetic effects (A), shared/common environmental effects (C) and non-shared environmental effects (E), which also includes measurement error (Plomin et al., 2013). Shared environmental effects are those environmental influences that contribute to the similarity between twins, whereas non-shared environments are those environmental influences that make twins dissimilar, such as individual-specific life events. The total variance of a trait can therefore be defined as V=A+C+E.

Since MZ twin pairs share 100% and DZ twin pairs share on average 50% of their genome, they have genetic correlations of 1 and .5, respectively. Since both MZ and DZ twin pairs share their environments to a very similar extent, such as sharing the same prenatal environment and growing up in the same family environment, the correlation between twins' shared environments can be assumed to be 1 for both MZ and DZ twin pairs (the equal environments assumption). Similarity/correlation between MZ twin pairs (rMZ) therefore can be defined as rMZ = 1A + 1C, and for DZ twin pairs as rDZ = 0.5*A + 1C. The correlation between the MZ pairs (rMZ) includes all genetic effects and all shared environmental effects: rMZ = 1A + 1C. For DZ twins, the correlation (rDZ) reflects only half of the genetic effects, but all shared environmental effects: rDZ = 0.5*A + 1C. Higher phenotypic similarity within MZ twin pairs, in comparison to DZ twin pairs, can therefore be attributed to MZ twins' higher genetic similarity (A). Using A+C+E=V, it is possible to calculate the proportional contribution of A, C and E to the total variance in a trait (V=1). The extent of genetic influences on a trait (heritability h^2) can be estimated broadly by doubling the difference between the MZ and DZ correlations: A= 2(rMZ – rDZ). E is what makes twins different from one another and is estimated as the difference between the MZ twin correlations and 1: E= 1-rMZ. Since C also contributes to the higher resemblance between MZ twin pairs, any variance not accounted for by A and E can be attributed to C (C= 1 – A+E). If the MZ correlation is more than twice the DZ correlation, non-additive genetic effects, such as dominance (D) are indicated. The C component can be replaced by D, where rMZ= 1A+1D and rDZ= .5*A+.25*D. Since the heritability estimate is derived as a ratio of variance components, the heritability estimate always lies between 0 and 1.

Commonly, path analyses and structural equations are used to estimate the A, C and E components. Using Wright's rules of path analysis (Wright, 1920), the predicted covariance and variance of the phenotype for DZ and MZ pairs are estimated by path tracing. The total variance is calculated as the sum of the squared coefficients of the latent factors (a^2+ c^2+e^2), and MZ and DZ twin pair covariance is calculated by including all A and C paths connecting the pairs (covMZ= a^2+ c^2, covDZ = .5*a^2+ c^2). The relationship between the A, C and E components for twin pairs are illustrated in **Figure 3.1**. Maximum Likelihood Structural Equation Modelling (MLSEM) is typically used to provide ACE estimates and goodness-of-fit statistics. This is done by first fitting a saturated model to the data (i.e. a model with no parameter constraints and which includes observed means, variance and covariance), before fitting a constrained model that tests the assumptions of twin models, by equating means and variance within and

across pairs. Next, an ACE model is fitted to the data, estimating the "a", "c" and "e" parameters from predicted variance and covariance. The fit of the ACE model is compared to the saturated model to assess its goodness-of-fit, according to their log-likelihood statistic (-2ll). ACE sub-models can also be constructed by constraining the A and/ C parameters to zero, and their fit compared to the full ACE model to determine the best fitting model, based on the principle of parsimony (model with fewer parameters) and using information criterions such as Bayesian Information Criterion (BIC) or Akaike's Information Criterion (AIC). E parameter is always included because it contains measurement error.

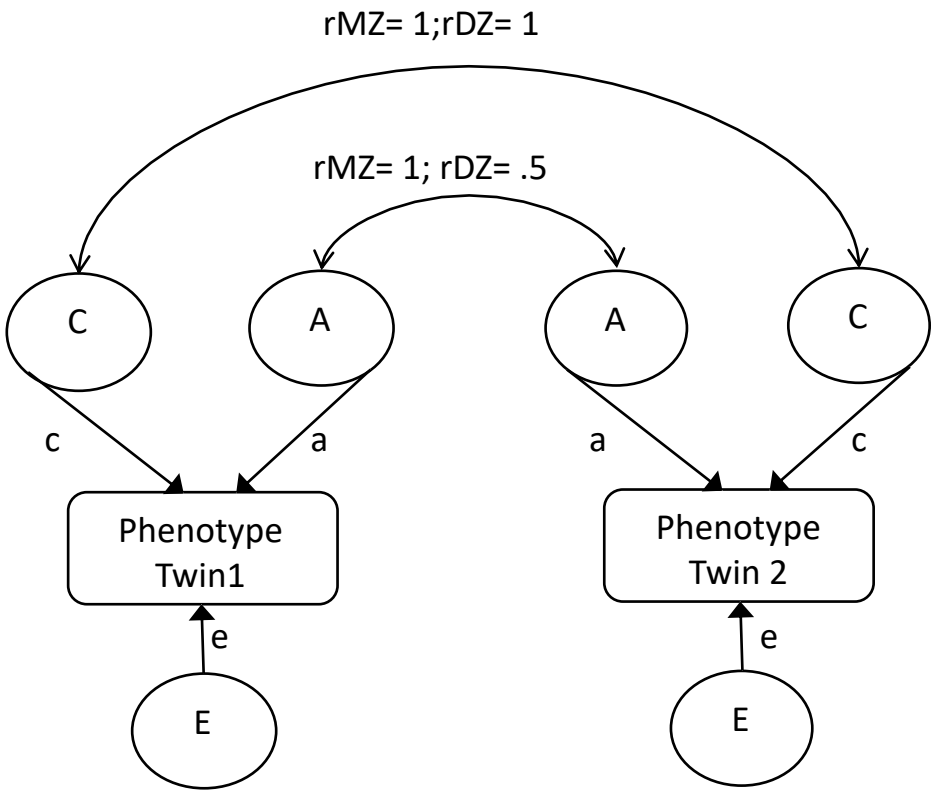


Figure 3.1 Path diagram representing the relationship between the A, C, and E latent factors for MZ and DZ twins.
Latent variables: A (additive genetics effects), C (shared environmental effects) and E (non-shared environmental effects). The single headed arrows indicate causal pathways from latent factors, denoted as "a", "c" and "e". Double headed arrows show the correlation between the latent factors between the two twins (rMZ and rDZ). Non-shared environmental factors are unique to each twin and therefore not correlated between the two twins.

The ACE models can be further extended to include more than one phenotype, to examine whether correlations between phenotypes are due to shared genetic or environmental influences. Depending on the specific aim of the researcher, three main types of model may be examined for this purpose: Cholesky decomposition, independent pathway or common pathway models. In all these bivariate/multivariate models, cross-twin cross-trait correlations for the phenotypes of interest are compared in MZ and DZ pairs. The Cholesky decomposition-correlated factors model assumes that the phenotypic correlation between variables is due to correlating ACE influences. Higher cross-twin cross-trait correlations in MZ twins compared to DZ twins indicate that genetic effects underlie the phenotypic correlations. On the other hand, if the cross-twin cross-trait correlations are similar for both MZ and DZ pairs, shared environmental effects are implicated. Significant within-individual cross-trait correlations but non-significant cross-twin cross-traits correlation indicate that E factors are involved. The independent pathway and the common pathway models parse the variance/covariance of the phenotypes of interest into two sets of ACE effects: those that are due to shared ACE effects and those that are due to specific ACE effects for each phenotype. However, the common pathway model assumes that the shared ACE factors influence the variables of interest via a single psychometric/latent liability factor.

Another extension of the classic univariate twin model is to test for differences between males and females in the source or extent of genetic and environmental contribution to variability in a trait (Neale & Cardon, 1992). To examine this, the sample can be split into same sex: MZ male (MZM), MZ female (MZF), DZ male (DZM), DZ female (DZF) or opposite sex twin pairs: DZOS. If the observed correlation for DZOS is much smaller than the correlation for same sex DZ twins, this may indicate "qualitative" sex differences, such that the *sources* of genetic or environmental effects underlying the trait are different for males and females. On the other hand, a different MZM:DZM vs. MZF:DZF correlation ratio indicates the presence of "quantitative" sex differences, such that the *extent* of genetic and environmental influences are different for males and females. The qualitative sex differences are tested in a *full heterogeneity model*, by constructing two models, in one of which the shared environmental correlation (r_c) between DZOS is fixed to its theoretical value (r_c=1) and the genetic correlation (r_g) is left to be estimated freely, and another model the reverse (r_c=free, r_g= .5), to estimate A, C, E. The quantitative sex differences are tested in a *heterogeneity model*, by fixing both r_c and r_g values and allowing the ACE estimates to be free for males and females. Another possible variation between males and females may be due to male and female

differences in the phenotypic variance, as indicated by differences in the mean and variance. The so called "scalar" sex differences test includes a scalar term, in a *phenotypic scalar* model, to correct for phenotypic variance differences between males and females, but no differences in ACE influences. Finally, the *homogeneity* model assumes no sex differences exist by equating all parameter estimates for males and females. The fit of these sex-limitation models are compared to each other to determine the best-fitting model and the presence of the type of sex differences, if any exist.

To address the first aim of this chapter, a univariate ACE model was used to estimate the heritability of environmental sensitivity and its three components. An ADE model was also constructed and examined against the ACE model to determine the best-fitting model. In addition, sex differences in the heritability estimates were examined, using the main four sex-limitation models as described above: a) *qualitative* sex differences, which examines differences in the sources of variation in males and females; b) *quantitative* sex differences, which examines differences in the extent of influence of ACE parameters in males and females; c) no sex differences but with *phenotypic scalar*, which includes a term to correct for phenotypic variance differences between males and females, but no differences in ACE influences between males and females; d) *homogeneity* model, a reduced parameter model, where no sex differences exist in ACE estimates.

To address the second aim, a multivariate common pathway ACE model (as well as a Cholesky Decomposition ACE model-correlated factors solution, for comparison) was constructed to examine the genetic architecture of sensitivity as a function of its three components.

To address the third aim, multivariate independent pathway ACE models were constructed to examine the extent to which the phenotypic correlations between environmental sensitivity and the Big Five personality traits, and between environmental sensitivity and depression and anxiety, are due to common or specific genetic influences.

The structural equation modelling package of OpenMx (Boker et al., 2011) in R (www.R-project.org) was used to conduct all twin analyses. Raw data maximum likelihood was used for model-fitting and minus twice the log likelihood (-2ll) was used to assess the goodness-of-fit of models. To assess the overall fit of the ACE genetic model, its -2ll was compared to that of a fully saturated model (a model that describes

the raw data using maximum number of free parameters). The best-fitting genetic model (AE, CE, E) was examined based on lowest -2ll, the principle of parsimony and AIC by comparing it to the full ACE model. A difference in AIC between two models of 2 or less provides equivalent support for both models, in which case the most parsimonious model (i.e. with lowest number of parameters) was chosen. A difference of 3 indicates that the lower AIC model has considerably more support, and a difference of more than 10 indicates that the lower AIC model is a substantially better fit, compared to the higher AIC model (Burnham & Anderson, 2004)

Data Analysis steps: First, descriptive statistics of the sample were examined by selecting a subset of the sample, including only one twin from each pair (randomized order).

Second, all variables were residualised for age and gender (McGue & Bouchard, 1984) and the interclass correlation coefficients were obtained for MZ, DZ, DZS and DZO twin pairs. ACE univariate twin analysis with the sex limitation models estimated the heritability of environmental sensitivity and its three components and investigated sex differences in ACE estimates. ACE univariate models were also used to estimate the heritability of depression, anxiety and the Big Five personality traits.

Third, a common pathway model was fitted to the data to examine the relationship between the three subscales of environmental sensitivity. A Cholesky decomposition correlated factors solution model was also fitted to the data to compare its fit to the common pathway model.

Finally, an independent pathways model was fitted to the data to examine a) the shared aetiology of environmental sensitivity and the Big Five, as well as b) the shared aetiology of environmental sensitivity and depression and anxiety.

3.2.3 Power analysis

Statistical power in twin studies is dependent on several factors, including sample size, MZ:DZ twin ratios, type of data (continuous versus categorical) and the proportion of variance due to A (additive genetic influences) or C (common environmental influences) components (Verhulst, 2017; Visscher, 2004). Verhulst (2017) examination of statistical power in univariate ACE twin design indicates a study would have sufficient power (> 80%) to detect significant ACE estimates for a moderately heritable quantitative trait (~30%) if the sample size is over 1000 twins. Power is evaluated for A

and C estimates only, since E is arrived at by subtracting the A+C estimate from total variance=1. The MZ:DZ sample ratio of 1:1 provides the best power to detect a significant A component. A larger proportion of DZ relative to MZ twins increases the power to detect the C component; however, an imbalance towards higher DZ ratio reduces the power to detect A.

As shown in **Figure 3.2a** (adapted from Verhulst, 2017), with sample sizes of over 500 twin pairs, there is more than 80% power to detect A influences of .1 and over 90% to detect larger A influences. In order to detect similarly-sized C influences, larger samples are needed, with sample sizes of 600 twin pairs providing over 80% power and 1000 twin pairs over 90% power. The effects of MZ:DZ ratios on the power are presented in **Figure 3.2b** (adapted from Verhulst, 2017). The results indicate that a balanced (MZ:DZ ratio of 1:1) sample of 600 twins provided over 90% power to detect A influences; however, for an imbalanced MZ:DZ ratio (1:5), a larger sample of 700 is required to provide over 80% power. Similar ratios provide over 80% power to detect C influences in smaller samples of 400 twin pairs.

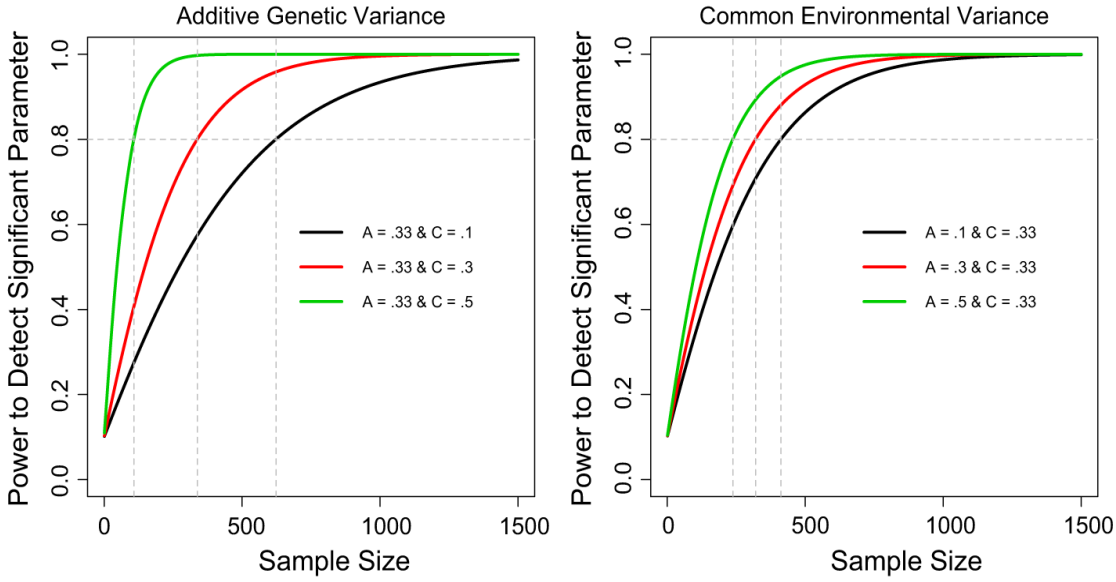


Figure 3.2a Power analysis for the additive genetic (left panel) and common environmental variance components (right panel), as a function of A or C components. Adapted from "A Power Calculator for the Classical Twin Design" Figure 2 by B. Verhulst, 2017, *Behavior Genetics, 47*(2), 255-261. Copyright 2017 by Springer Nature.

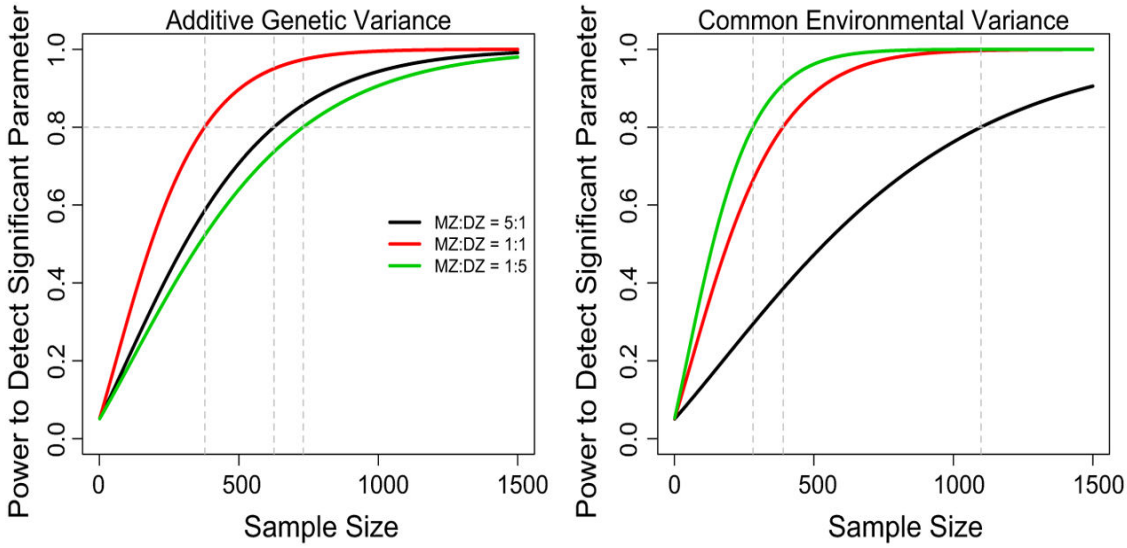


Figure 3.2b Power analysis for the additive genetic and common environmental variance components as a function of the ratio of MZ to DZ twins. Adapted from "A Power Calculator for the Classical Twin Design" Figure 3 by B. Verhulst, 2017, *Behavior Genetics, 47*(2), 255-261. Copyright 2017 by Springer Nature.

Univariate ACE models that incorporate sex limitation models require larger sample sizes (>10000). This is especially so if the genetic correlation between males and females is high in a qualitative sex differences model, or when the differences for A estimates in males and females are small in a quantitative sex limitation model. For larger effects, samples of 5000 and above provide sufficient power. An example of power in sex limitation models is presented in **Figure 3.2c** (adapted from Verhulst, 2017).

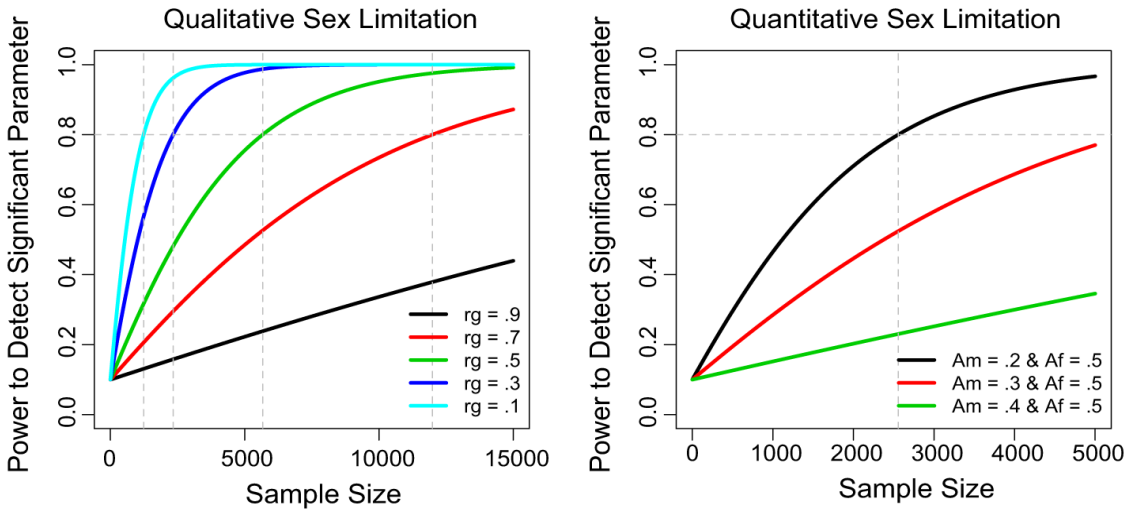


Figure 3.2c Power analysis for qualitative and quantitative sex limitation models. Adapted from "A Power Calculator for the Classical Twin Design" Figure 6 by B. Verhulst, 2017, *Behavior Genetics, 47*(2), 255-261. Copyright 2017 by Springer Nature.

Statistical power to detect a significant genetic correlation (Rg) between two or more phenotypes depends on the magnitude of the genetic influence on each trait, as well as the magnitude of their genetic correlation. As shown in **Figure 3.2d** (adapted from Verhulst, 2017), power increases as Rg and A increase. When Rg and A estimates are medium or large (~ .3 and .5), a sample of 500 twins provide sufficient power to detect significant genetic correlations, but for smaller effects (~.1) sample sizes of over 2000 are required.

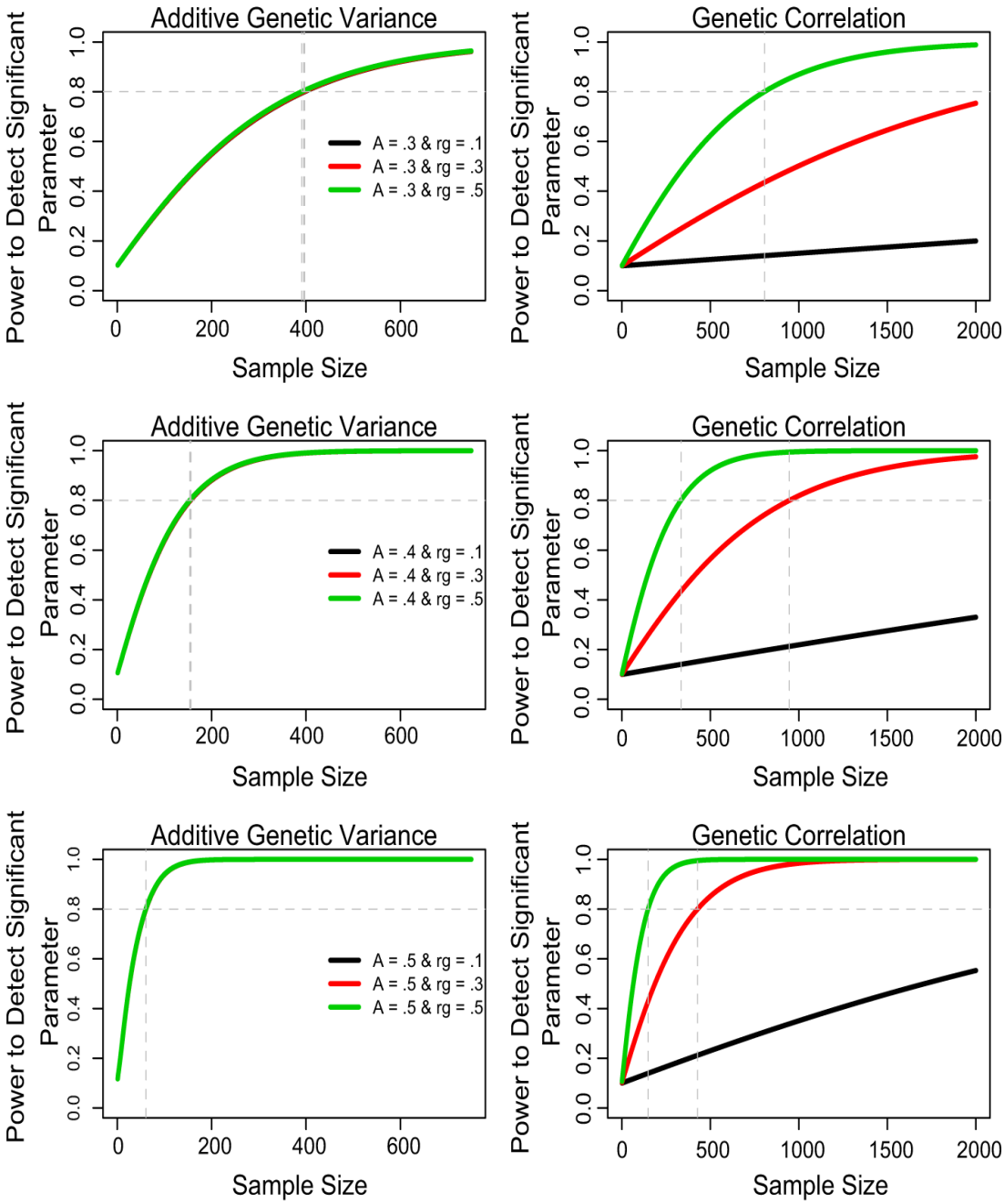


Figure 3.2d Power analysis for genetic correlation between two phenotypes. Adapted from "A Power Calculator for the Classical Twin Design" Figure 5 by B. Verhulst, 2017, *Behavior Genetics, 47*(2), 255-261. Copyright 2017 by Springer Nature.

The data in the current chapter included continuous data (HSC scores) on 1434 twin pairs with a MZ:DZ ratio of 1:3. The heritability of environmental sensitivity is expected to be moderate, given a recent study by Polderman et al. (2015) showed most human traits are moderately heritable. The current sample was therefore sufficiently (> 90%) powered to detect the genetic and environmental influences in a univariate ACE model, and medium to large genetic correlations in multivariate models. The sample is, however, underpowered to detect small sex differences in the estimates.

3.3 Results

3.3.1 Descriptive statistics

Descriptive statistics, including information on the sample size, mean scores and bivariate correlations for all measures, are presented in **Table 3.1**. Females scored significantly higher than males on all sensitivity measures (total score of environmental sensitivity: $F_{(1,1435)} = 48.58$, $p < .001$; EOE: $F_{(1,1435)} = 25.56$, $p < .001$; AES: $F_{(1,1435)} = 14.64$, $p < .001$; LST: $F_{(1,1435)} = 54.42$, $p < .001$) and personality measures of neuroticism ($F_{(1,561)} = .16.93$, $p < .001$), agreeableness ($F_{(1,558)} = 11.40$, $p < .001$) and conscientiousness ($F_{(1,560)} = 7.09$, $p < .05$). Mean differences were not statistically significant for openness ($F_{(1,560)} = .06$, $p = .81$) and extraversion ($F_{(1,560)} = .10$, $p = .32$). Anxiety and depression scores were also significantly higher for females than males ($F_{(1,1433)} = 130.13$, $p < .001$; $F_{(1,1434)} = 44.22$, $p < .001$, respectively). Age was not significantly correlated with any of the variables, except for AES ($r = .09$, $p < .001$).

Table 3.1 Descriptive statistics of the study sample and all variables

	Sample	Mean (SD)		Bivariate correlations									
		Male	Female	ES	EOE	AES	LST	N	O	C	E	A	Dep
HSC	2868	45.16 (10.95)	49.23 (10.86)										
Ease of Excitation	2868	17.77 (6.57)	19.55 (6.56)	**.88****									
Aesthetic Sensitivity	2868	20.30 (4.21)	21.11 (3.57)	**.58****	**.27****								
Low Sensory Threshold	2868	7.10 (3.70)	8.61 (4.00)	**.73****	**.52****	**.17****							
Neuroticism	1156	14.97 (4.20)	16.42 (4.17)	**.33****	**.39****	-.02	**.24****						
Openness	1154	21.21 (3.90)	21.53 (3.57)	.06	-.02	**.19****	.01	-.02					
Conscientiousness	1150	21.81 (3.73)	22.68 (3.96)	-.05	**-.13****	**.14****	-.03	**-.16****	**.17****				
Extraversion	1154	21.53 (4.32)	21.45 (3.89)	**-.18****	**-.24****	**.13****	**-.21****	**-.38****	**.27****	**.29****			
Agreeableness	1152	21.18 (3.89)	22.31 (4.02)	.01	-.04	.07	.04	**-.19****	**.22****	**.35****	**.24****		
Depression	2868	3.68 (4.40)	5.49 (5.95)	**.34****	**.37****	**.09****	**.24****	**.45****	.03	**-.17****	**-.26****	**-.11***	
Anxiety	2868	24.93 (5.40)	28.58 (6.70)	**.42****	**.42****	**.17****	**.32****	**.37****	.08	-.02	**-.17****	-.03	**.49****

HSC=Highly Sensitive Child scale; EOE = Ease of Excitation; AES = Aesthetic Sensitivity; LST = Low Sensory Threshold; SD = standard deviation; N = Neuroticism; O = Openness; C = Conscientiousness; E = Extraversion; A = Agreeableness; Dep= Depression; Means and bivariate correlations represent the data from a sample of one randomly selected twin from each pair, to ensure data is not influenced by family relatedness. Bivariate correlations represent variables corrected for age and sex; * $p < .01$; ** $p < .001$

3.3.2 The heritability of environmental sensitivity

Cross-twin correlations from the univariate ACE model showed evidence of genetic influences on variability in all traits, with MZ twin correlations being larger than DZ twin correlations in both males and females (**Table 3.2**). Twin correlations differed across male and female pairs for all variables, but the overlapping confidence intervals indicated that these differences may not be significant.

The univariate ACE analyses, including the sex-limitation model-fitting results, showed no significant evidence of sex differences for environmental sensitivity or EOE component; a no sex differences model was the best-fitting, when compared to other models, according to a lower AIC. A slightly better fit, of the phenotypic scalar model, for LST and AES components was found. **Table 3.3** shows the model fit summary results of all univariate ACE models for HSC and its three components. The results indicated no significant differences between sexes in ACE estimates for HSC and its three components (see **Appendix 3.1** for ACE estimates from all models). The ACE estimates from the best-fitting sex limitation model for HSC and its three components, as well as estimates for personality traits, depression and anxiety are presented in **Table 3.4**. (see **Appendix 3.1** for personality, depression and anxiety ACE model fit results). The results indicated that the heritability of HSC was 47% (95%CI = 30, 53), with no evidence of shared environmental influences. The remaining 53% (95%CI =47, 59) of the variation was due to non-shared environmental influences, which also includes measurement error.

Comparing the ACE model fit to its sub models (AE, CE, E) indicated that the AE model was the most parsimonious, with no deterioration in fit compared to the full model (Δ -2ll =.0004, p= .98). In order to examine dominant genetic effects, an ADE model was compared to the ACE model, but it was not found to be a better fit to the data (Δ -2ll =.0004, p= .98; parameter estimates: A= .48 95%CI [.42, .56]; D= .00 95%CI [.00,.27]; E= .52 95%CI [.47, .58]), suggesting additive genetic influences sufficiently captured the heritability of HSC.

Table 3.2 Univariate cross-twin correlations for HSC and its three components, personality traits, depression, and anxiety

	MZ	DZ	MZM	DZM	MZF	DZF	DZOS
HSC	.47 (.41, .53)	.24 (.18, .30)	.53 (.42, .61)	.24 (.10, .37)	.45 (.36, .52)	.26 (.14, .36)	.22 (.14, .30)
Ease of Excitation	.42 (.32, .49)	.22 (.15, .27)	.48 (.36, .58)	.35 (.22, .46)	.40 (.30, .48)	.27 (.15, .38)	.14 (.06, .23)
Aesthetic Sensitivity	.39 (.32, .46)	.13 (.09, .20)	.42 (.30, .51)	.04 (-.10, .17)	.37 (.27, .45)	.19 (.07, .29)	.15 (.06, .24)
Low Sensory Threshold	.41 (.34, .48)	.19 (.13, .25)	.48 (.36, .58)	.26 (.12, .39)	.39 (.27, .47)	.25 (.13, .35)	.13 (.04, .22)
Neuroticism	.33 (.21, .43)	.12 (.00, .23)	.30 (.01, .50)	.19 (-.05, .40)	.34 (.21, .45)	.13 (-.09, .33)	.08 (-.09, .24)
Openness	.40 (.29, .50)	.07 (-.04, .19)	.32 (.09, .51)	.04 (-.20, .26)	.43 (.30, .54)	.13 (-.06, .31)	.06 (-.12, .23)
Conscientiousness	.32 (.19, .43)	.04 (-.07, .15)	.11 (-.12, .33)	.01 (-.27, .28)	.42 (.27, .53)	.03 (-.14, .20)	.06 (-.12, .23)
Extraversion	.35 (.24, .45)	.24 (.12, .35)	.25 (.02, .44)	.20 (-.08, .43)	.39 (.26, .50)	-.08 (-.31, .17)	.39 (.25, .51)
Agreeableness	.27 (.14, .38)	.09 (-.03, .20)	.15 (-.09, .36)	.02 (-.26, .29)	.32 (.17, .45)	.09 (-.07,.24)	.12 (-.08, .29)
Depression	.39 (.32, .46)	.22 (.16, .28)	.30 (.18, .41)	.21 (.07, .34)	.44 (.35, .52)	.38 (.27, .47)	.12 (.03, .21)
Anxiety	.45 (.38, .51)	.19 (.13, .25)	.43 (.30, .53)	.27 (.13, .40)	.47 (.38, .54)	.21 (.08, .31)	.17 (.09, .25)

MZ = monozygotic twins; DZ = dizygotic twins; MZM = monozygotic male twins; MZF = monozygotic female twins; DZM = dizygotic male twins; DZF = dizygotic female twins; DZOS=dizygotic opposite sex twins; CI = 95% Confidence Interval. CIs not including 0 indicate significant estimates and non-overlapping CIs indicate significant difference between the estimates; Twin correlations represent variables corrected age and sex. The MZ correlations more than twice the DZ correlations suggest that genetic influences should be interpreted as both additive and non-additive effects.

Table 3.3 Univariate ACE sex limitation models fit summary for HSC and its three components

	Model name (number)	Model fit									
		Compared to fully saturated Model						Compared to sex limitation models			
		-2ll	df	AIC	Δ -2ll	Δ df	*p*	Comparison model	Δ -2ll	Δ df	*p*
HSC	1 Fully saturated	21736.95	2843	16050.95							
	2 Constrained	21752.89	2859	16034.89	15.95	16	.46				
	3 Qualitative, r_g= free	21752.98	2859	16034.98	16.03	16	.45				
	4 Qualitative, r_c= free	21752.98	2859	16034.98	16.03	16	.45				
	5 Quantitative, r_g= .5 & r_c=1	21752.98	2860	16032.98	16.03	17	.52	3 & 4	.00	1	1
	6 Scalar	21851.44	2862	16127.439	114.49	19	< .001	5	98.46	2	< .001
	7 Homogeneity	**21756.23**	**2864**	**16028.23**	**19.28**	**21**	**.57**	6	**-95.21**	**2**	**1**
Ease of Excitation	1 Fully saturated	18871.71	2843	13185.71							
	2 Constrained	18889.26	2859	13171.26	17.55	16	.35				
	3 Qualitative, r_g= free	18889.33	2859	13171.33	17.62	16	.35				
	4 Qualitative, r_c= free	18889.26	2859	13171.26	17.55	16	.35				
	5 Quantitative, r_g= .5 & r_c=1	18890.38	2860	13170.38	18.67	17	.35	3 & 4	1.12	1	.30
	6 Scalar	18898.34	2862	13174.34	26.63	19	.11	5	7.96	2	.02
	7 Homogeneity	**18901.46**	**2864**	**13173.46**	**29.75**	**21**	**.10**	6	**3.12**	**2**	**.21**
Aesthetic Sensitivity	1 Fully saturated	15810.66	2843	10124.66							
	2 Constrained	15832.27	2859	10114.27	21.60	16	.16				
	3 Qualitative, r_g= free	15837.51	2859	10119.51	26.85	16	.04				
	4 Qualitative, r_c= free	15837.66	2859	10119.66	27	16	.04				
	5 Quantitative, r_g= .5 & r_c=1	15837.66	2860	10117.66	27	17	.06	3 & 4	.15	1	.70
	6 Scalar	**15837.89**	**2862**	**10113.89**	**27.23**	**19**	**.10**	5	**.23**	**2**	**.89**
	7 Homogeneity	15864.50	2864	10138.50	53.84	21	< .001	6	26.61	2	< .001

Table 3.3 Continued

Model name (number)		Model fit									
		Compared to fully saturated Model						Compared to sex limitation models			
		-2ll	df	AIC	Δ -2ll	Δ df	*p*	Comparison model	Δ -2ll	Δ df	*p*
Low Sensory Threshold	1 Fully saturated	15871.03	2843	10185.03							
	2 Constrained	15878.88	2859	10160.88	7.86	16	.95				
	3 Qualitative, r_g= free	15878.89	2859	10160.89	7.86	16	.95				
	4 Qualitative, r_c= free	15878.88	2859	10160.88	7.85	16	.95				
	5 Quantitative, r_g= .5 & r_c=1	15878.89	2860	10158.89	7.86	17	.97	3 & 4	.01	1	.95
	6 Scalar	**15884.53**	**2862**	**10160.53**	**13.5**	**19**	**.81**	5	**5.64**	**2**	**.06**
	7 Homogeneity	15899.83	2864	10171.83	28.8	21	.12	6	15.30	2	< .001

Fully saturated model=model with maximum number of parameters describing the data; Constrained = sub-model of the fully saturated model, testing the assumptions of twin design, with means and variances equated across twins and zygosity; Qualitative ACE (r_g=Free) and Qualitative ACE (r_c=Free) = models that allow differences in source of variation in males and females, where either r_c or r_g is free to be estimated for opposite sex twin pairs and can vary below the values assigned to same-sex dizygotic pairs; Quantitative ACE =model that allows differences in the extent of influence of ACE parameters in males and females, with r_c and r_g in opposite sex twins being fixed to 1 and .5 respectively, estimating the ACE parameters from same sex twin pairs only; Scalar = model with no sex differences in ACE parameters but scalar term on males; Homogeneity= univariate ACE model with no difference between males and females;−2ll= minus twice the log likelihood; df= degrees of freedom; AIC= Akaike's information criterion; Δ -2ll =difference in -2ll value; Δ df= difference in degrees of freedom; p= p-value; The best fitting models are marked as bold, selected based on the principle of parsimony and lowest AIC and -2ll value. A difference in AIC between two models of 2 or less, provides equivalent support for both models, in which case the most parsimonious model (i.e. with lowest number of parameters) was chosen, a difference of 3 indicates that the lower AIC model has considerably more support, and a difference of more than 10, indicates that the lower AIC model is a substantially better fit compared to the higher AIC model.

Table 3.4 Univariate heritability estimates for HSC and its three components, personality traits, depression, and anxiety

	Variance Components (95% CI)		
	A	C	E
HSC	.47 (.30, .53)	.00 (.00, .13)	.53 (.47, .59)
Ease of Excitation	.42 (.23, .48)	.01 (.00, .14)	.58 (.52, .65)
Aesthetic Sensitivity	.36 (.25, .42)	.00 (.00, .07)	.64 (.58, .71)
Low Sensory Threshold	.41 (.27, .47)	.00 (.00, .00)	.59 (.53, .65)
Neuroticism	.31 (.08, .41)	.00 (.00, .18)	.69 (.59, .79)
Openness	.35 (.24, .45)	.00 (.00, .00)	.65 (.55, .76)
Conscientiousness	.26 (.10, .37)	.00 (.00, .11)	.74 (.63, .85)
Extraversion	.22 (.00, .45)	.13 (.00, .35)	.65 (.54, .76)
Agreeableness	.25 (.01, .35)	.00 (.00, .17)	.75 (.65, .87)
Depression	.38 (.20, .46)	.03 (.00, .16)	.59 (.53, .66)
Anxiety	.43 (.31, .49)	.00 (.00, .08)	.56 (.51, .63)

A = additive genetic influences; C = shared environmental influences; E = non-shared environmental influences; CIs not including 0 indicate significant estimates.

3.3.3 The genetic architecture of environmental sensitivity as a function of its three components

The higher MZ versus DZ cross-twin cross-trait correlations, as shown in **Table 3.5**, indicate that genetic influences contribute to the correlation between all three components of environmental sensitivity.

Table 3.5 Cross-twin cross- trait correlations for the three components environmental sensitivity

	MZ correlations	DZ correlations
AES - EOE	.17 (.12, .31)	.10 (.05, .14)
LST - EOE	.26 (.20, .31)	.14 (.09, .19)
AES - LST	.13 (.07, .18)	.07 (.02, .12)

HSC: Highly Sensitive Child Scale; EOE = Ease of Excitation; AES = Aesthetic Sensitivity; LST = Low Sensory Threshold; MZ = monozygotic twins; DZ = dizygotic twins; 95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates.

The common pathway model examined how much of the variance in the three components of sensitivity are due to common (Ac) versus specific genetic effects (As). As expected from the univariate analysis results, the latent factor of environmental sensitivity, as captured by EOE, AES and LST, was heritable (51%, 95% CI= 29, 60), with EOE loading most strongly on the latent factor (.90, 95% CI= .83, .96), followed by LST (.58, 95% CI= .53, .63) and AES (.29, 95% CI = .25 - .33) (see **Figure 3.3**). The proportion of variance explained by common and specific genetic and environmental influences on the three components of environmental sensitivity are presented in **Table 3.6**. It was found that common genetic influences explained 42% (95% CI=23, 48) of the variance in EOE, 17% (95% CI= 10, 22) in LST and 4% (95% CI= 2, 6) in AES. Once common genetic influences were accounted for, there was no evidence of genetic influences specific to EOE, but 29% (95% CI= 20, 35) and 24% (95% CI= 15, 29) of the variation in AES and LST were explained by genetic influences specific to each component. This means that, whilst genetic influences on the heritability of EOE component were mainly explained by common genetic influences on the latent factor, only 12% of the genetic influences on AES (calculated as 4/33) and 41% of the genetic influences on LST (calculated as 17/41) were explained by common influences. The

remaining heritability in AES and LST was due to genetic influences specific to each component (LST: 58% and AES: 88%).

Common, non-shared environmental influences (Ec) explained 39% (CI= 30, 50) of the variance in EOE, and 16% (CI= 13, 21) and 4% (CI= 3, 5) of the variance in LST and AES, respectively. Specific, non-shared environmental influences explained 18% (CI= 9, 27), 63% (CI= 56, 69) and 42% (CI= 37, 48) in EOE, AES and LST, respectively. This means that, of the total non-shared environmental influences on each component, 31% of the variance in EOE (calculated as 18/57), 72% of the variance in LST (calculated as 42/58) and 94% of the variance in AES (calculated as 63/67) was due to environmental factors specific to each component.

The small, non-significant effect of shared environmental influences (C) on environmental sensitivity was due to common environmental influences in the EOE component specific to environmental sensitivity (Cs= .01 95% CI= .00, .14).

A Cholesky decomposition correlated factors solution was also fitted to the data to compare its fit to the common pathway model (See **Appendix 3.3** for results). The common pathway model showed a better fit, as indicated by a lower AIC value, suggesting that a general factor of environmental sensitivity captures the relationship between the three components better than three separate correlating factors (see **Table 3.7**)

Overall, the results indicate that there are common genetic and environmental influences that underlie all three components of sensitivity, contributing to a general factor of environmental sensitivity. At the same time, the results also indicate that there are some genetic and environmental influences on the LST and AES components that specifically explain variations in these components of environmental sensitivity.

Table 3.6 Shared and specific ACE influences on the three components of environmental sensitivity

	Common ACE influences			Specific ACE Influences			Total - Common ACE	Total- Specific ACE
	Ac	Cc	Ec	As	Cs	Es		
Ease of Excitation	.42 (.23, .48)	.01 (.00, .14)	.39 (.30, .50)	00 (.00, .00)	.00 (.00, .00)	.18 (.09, .27)	.82	.18
Aesthetic Sensitivity	.04 (.02, .06)	.00 (.00, .01)	.04 (.03, .05)	.29 (.20, .35)	.00 (.00, .01)	.63 (.56, .69)	.08	.92
Low Sensory Threshold	.17 (.10, .22)	.00 (.00, .06)	.16 (.13, .21)	.24 (.15, .29)	.00 (.00, .01)	.42 (.37, .48)	.33	.66

Ac = common A influences; Cc = common C influences; Ec = common E influences; As = specific A influences; Cs = specific C influences; Es = specific E influences; 95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimate; Total common and specific ACE effects are arrived at by adding up all common ACE and all specific ACE effects, making up total variance =1

Table 3.7 Common pathway and Cholesky correlated factors solution model fit summary

	Models Fit				Compared to Saturated Model			Compared to Cholesky		
	Parameters	-2ll	df	AIC	Δ -2ll	Δ df	*p*	Δ -2ll	Δdf	*p*
Fully saturated	135	49427.65	8469	32489.65						
Constrained	48	49504.15	8556	32392.15	76.50	87	.78			
Cholesky correlated factors	26	49544.76	8578	32388.76	117.10	109	.28			
Common pathway	23	49550.72	8582	32386.72	123.07	113	.24	5.97	4	.20

Constrained= The saturated model constrained to have the same mean and SD across twin and zygosity; −2ll= minus twice the log likelihood; df= degrees of freedom AIC= Akaike's information criterion; Δ -2ll =difference in -2LL value; Δ df= difference in degrees of freedom; p= p-value

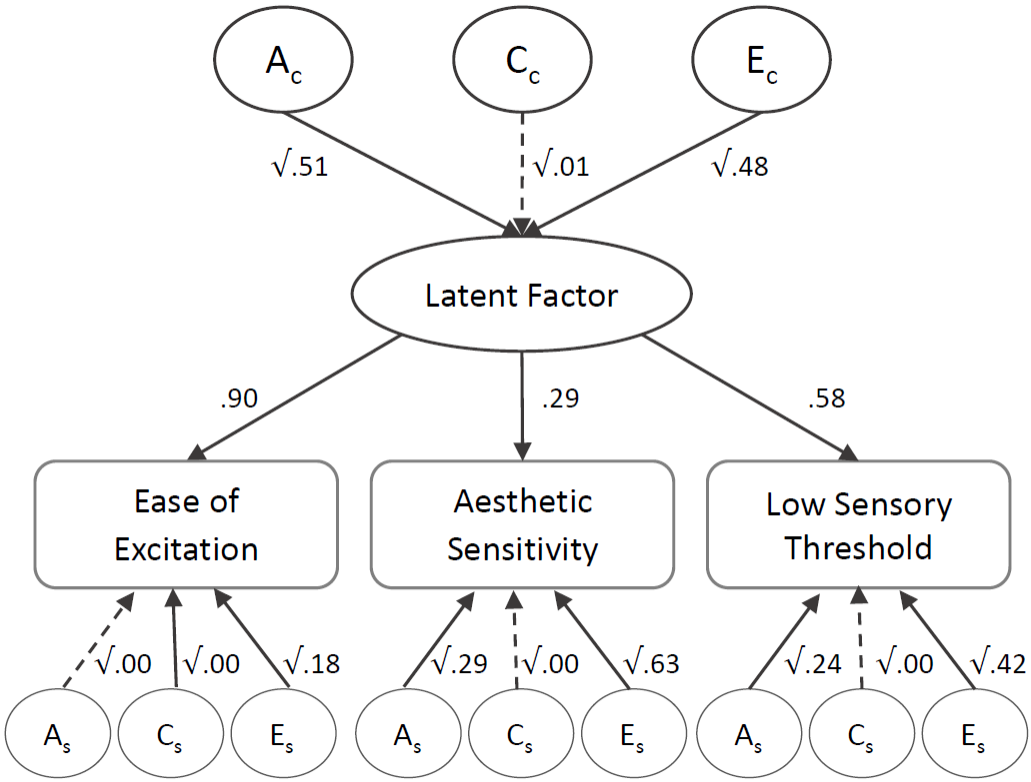


Figure 3.3 Common pathway model, showing shared and specific genetic and environmental influences on the three components of sensitivity

Ac = common additive genetic influences; Cc = Common shared environmental influences; Ec = common non-shared environmental influences. As = specific additive genetic influences; Cs = specific shared environmental influences; Es = specific non-shared environmental influences. The paths from common ACE influences to the latent factor represent the standardized ACE estimates for the latent factor of environmental sensitivity (A = .51, C = . 01, E = .48). The paths from the latent factor to the three components indicate the amount of variance explained in each component by the latent factor (Ease of Excitation = 90%, Aesthetic sensitivity = 29%), Low Sensory Threshold = 58%). The paths from specific ACE influences to the components represent the standardized ACE estimates that are specific to each component. Dashed lines represent non-significant path

3.3.4 Genetic overlap between environmental sensitivity and the Big Five personality traits, depression and anxiety

According to phenotypic correlations (see **Table 3.1**), HSC was positively correlated with depression (r = .34), anxiety (r = .42) and neuroticism (r = .33), and negatively with extraversion (r = -.18). Higher MZ: DZ ratios in the cross-twin cross-trait correlations between HSC and depression and anxiety indicated that the phenotypic correlations are due partly to shared genetic influences (See **Table 3.8**). Similar observations were made for HSC and neuroticism and extraversion. Lower MZ: DZ ratios for openness, conscientiousness and agreeableness suggested stronger environmental influences on their correlation with HSC. Independent pathway models were constructed to parse the proportion of variance on environmental sensitivity and personality traits, and depression and anxiety, to those genetic effects that are common to all traits (Ac) versus those that are specific to each trait (As), and to those environmental influences that are common to all traits (Cc/Ec) versus those that are specific to each trait (Cs/Es).

Table 3.8 Cross-twin cross-trait correlations for HSC and personality traits, depression, and anxiety

	MZ correlations	DZ correlations
	HSC	
Neuroticism	.29 (.21, .36)	.12 (.02, .22)
Extraversion	-.14 (-.06, -.22)	-.08 (.02, -.18)
Conscientiousness	-.11 (-.03, -.20)	-.07 (.04, -.17)
Openness	.12 (.04, .20)	.08 (-.03, .19)
Agreeableness	-.03 (.05, -.12)	-.05 (.07, -.15)
Depression	.23 (.18, .28)	.13 (.09, .17)
Anxiety	.30 (.25, .35)	.12 (.07, .17)

MZ = monozygotic twins; DZ = dizygotic twins; environmental correlation; 95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates

Environmental sensitivity and personality traits: The results of independent pathway analysis for environmental sensitivity and personality traits are presented in **Figure 3.4** and **Table 3.9**.

The results showed that common genetic influences (Ac) explained 36% (95% CI= 26, 51) and specific genetic influences accounted for 9% (95% CI= 0, 27) of the variation in

environmental sensitivity. This means that, of the total 45% heritability estimate (A) for environmental sensitivity in this model, 80% (calculated as 36/45) was due to genetic effects shared with personality traits (Ac), whereas the other 20% (calculated as 9/45) was due to genetic influences specific to environmental sensitivity (As). Common genetic influences accounted for the entirety of the genetic influences on neuroticism (Ac = 32%, 95% CI= 19, 42) and extraversion (Ac = 12%, 95% CI=2, 27), but did not make a significant contribution to the heritability of openness, conscientiousness or agreeableness. Therefore, the common genetic influences that explain individual differences in environmental sensitivity are mainly shared with the personality traits of neuroticism and extraversion (see **Figure 3.4**).

Common non-shared environmental influences (Ec) made a significant contribution to explaining the variance in all personality traits, but not in environmental sensitivity (Ec = .01, 95% CI= .00, .04). Environmental influences that explained the variance in environmental sensitivity were almost entirely (51/52=98%) due to non-shared environmental effects specific to this phenotype (Es= .51, 95% CI= 46, 59).

The small, non-significant effect of shared environmental influences on environmental sensitivity (C) was due to effects specific to environmental sensitivity (Cs=.02 95% CI= .00, .14).

Overall, these results suggest that the majority of the genetic influences that explain the heritability of environmental sensitivity are shared with the personality traits of neuroticism and extraversion, while the environmental influences that explain individual differences in environmental sensitivity are almost entirely specific to this phenotype. Of the total ACE influences on variations in environmental sensitivity, 37% was explained by those ACE effects shared with personality traits, and the remaining 63% were due to ACE effects specific to environmental sensitivity, indicating the shared, but largely distinct aetiology of environmental sensitivity and personality traits (see **Table 3.9**).

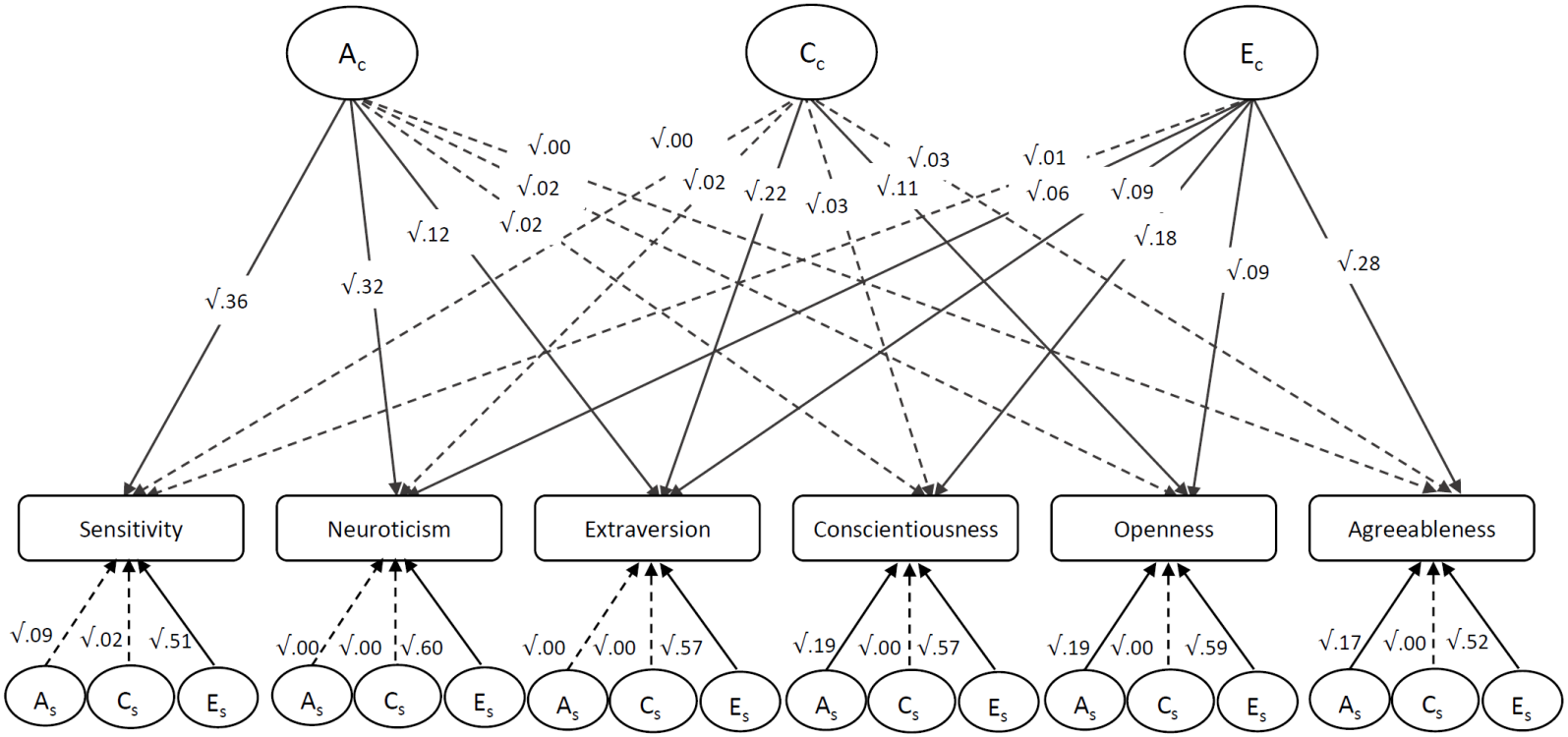


Figure 3.4 Independent pathway model, showing shared and specific genetic and environmental influences on environmental sensitivity and personality traits

Ac= common additive genetic influences; Cc= Common shared environmental influences; Ec= common non-shared environmental influences. As = specific additive genetic influences; Cs = specific shared environmental influences; Es= specific non-shared environmental influences. The paths from common ACE influences to environmental sensitivity and personality represent the standardized variance components explained by common ACE influences in each phenotype. The paths from specific ACE influences to environmental sensitivity and personality traits represent the standardized ACE estimates that are specific to each phenotype. Dashed lines represent non-significant paths.

Table 3.9 Shared and specific ACE influences on HSC and personality traits

	Common ACE influences			Specific ACE Influences			Total - Common ACE	Total- Specific ACE
	Ac	Cc	Ec	As	Cs	Es		
HSC	.36 (.26, .51)	.00 (.00, .07)	.01 (.00, .04)	.09 (.00, .27)	.02 (.00, .14)	.51 (.45, .58)	.37	.62
Neuroticism	.32 (.19, .42)	.02 (.00, .11)	.06 (.02, .13)	.00 (.00, .10)	.00 (.00, .00)	.60 (.51, .68)	.40	.60
Extraversion	.12 (.02, .27)	.22 (.08, .33)	.09 (.04, .16)	.00 (.00, .00)	.00 (.00, .00)	.57 (.48, .65)	.43	.57
Conscientiousness	.02 (.00, .07)	.03 (.00, .09)	.18 (.11, .27)	.19 (.06, .29)	.00 (.00, .01)	.57 (.46, .69)	.24	.76
Openness	.02 (.00, .09)	.11 (.04, .20)	.09 (.04, .16)	.19 (.05, .30)	.00 (.00, .00)	.59 (.49, .71)	.22	.78
Agreeableness	.00 (.00, .04)	.03 (.00, .08)	.28 (.18, .40)	.17 (.01, .27)	.00 (.00, .01)	.52 (.39, .65)	.31	.69

Independent pathway model fit summary: HSC and personality traits

	Model fit				Fit compared to the saturated model		
	Parameters	-2ll	df	AIC	Δ -2ll	Δ df	*p*
Fully Saturated	450	52397.45	8184	36029.45			
Constrained	165	52717.82	8469	35779.82	320.37	285	.07
Independent Pathway	48	52908.85	8586	35736.85	511.40	402	< .001

Ac = common A influences; Cc = common C influences; Ec = common E influences; As = specific A influences; Cs = specific C influences; Es = specific E influences; 95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimate; Total common and specific ACE effects are arrived at by adding up all common ACE and all specific ACE effects, making up total variance =1.

Fully saturated= model with maximum number of parameters describing the data; Constrained = the saturated model constrained to have the same mean and SD across twin and zygosity; −2ll= minus twice the log likelihood; df= degrees of freedom AIC= Akaike's information criterion; Δ -2ll =difference in -2LL value; Δ df= difference in degrees of freedom; p= p-value

Environmental sensitivity and depression and anxiety: The results of independent pathway analysis for environmental sensitivity and depression and anxiety are presented in **Figure 3.5** and **Table 3.10**.

The results showed that common genetic influences (Ac) explained 21% (95% CI= 18, 36) and specific genetic influences accounted for 24% (95% CI= 6, 31) of the variation in environmental sensitivity. This means that, of the total 45% heritability estimate (A) for environmental sensitivity in this model, 47% (calculated as 21/45) was due to common genetic effects (Ac) shared with depression and anxiety, whereas the other 53% (calculated as 24/45) were due to genetic influences specific to environmental sensitivity (As). Common genetic influences accounted for the entirety of the heritability of anxiety (Ac = 43%, 95% CI= 28, 49) and explained 22% (Ac = 12%, 95% CI= 12, 32) of the variance in depression. Therefore, the common genetic influences that explain individual differences in environmental sensitivity are mainly shared with anxiety and to a lesser degree with depression (see **Figure 3.5**).

Common non-shared environmental influences (Ec) explained 5% (CI= 2, 9) and specific non-shared environmental influences (Es) explained 48% (CI= 42, 54) of the variance in environmental sensitivity. This means that, of the total 53% of variance in environmental sensitivity due to non-shared environmental influences (E), 10% (5/53) were due to common E effects (Ec) and the remaining 90% due to specific E effects (Es).

The small, non-significant effect of shared environmental influences on environmental sensitivity (C) was due to shared environmental effects specific to environmental sensitivity (Cs= .03, 95% CI= .00, .14).

Overall, the results suggest that almost half of the genetic influences that explain variations in environmental sensitivity are shared with depression and anxiety, while the environmental influences that explain individual differences in environmental sensitivity are mainly specific to this phenotype. Of the total ACE influences on variations in environmental sensitivity, 29% was explained by those ACE effects shared with depression and anxiety, and the remaining 72% was due to ACE effects specific to environmental sensitivity, indicating the shared, but largely distinct aetiology of environmental sensitivity and depression and anxiety (see **Table 3.10**).

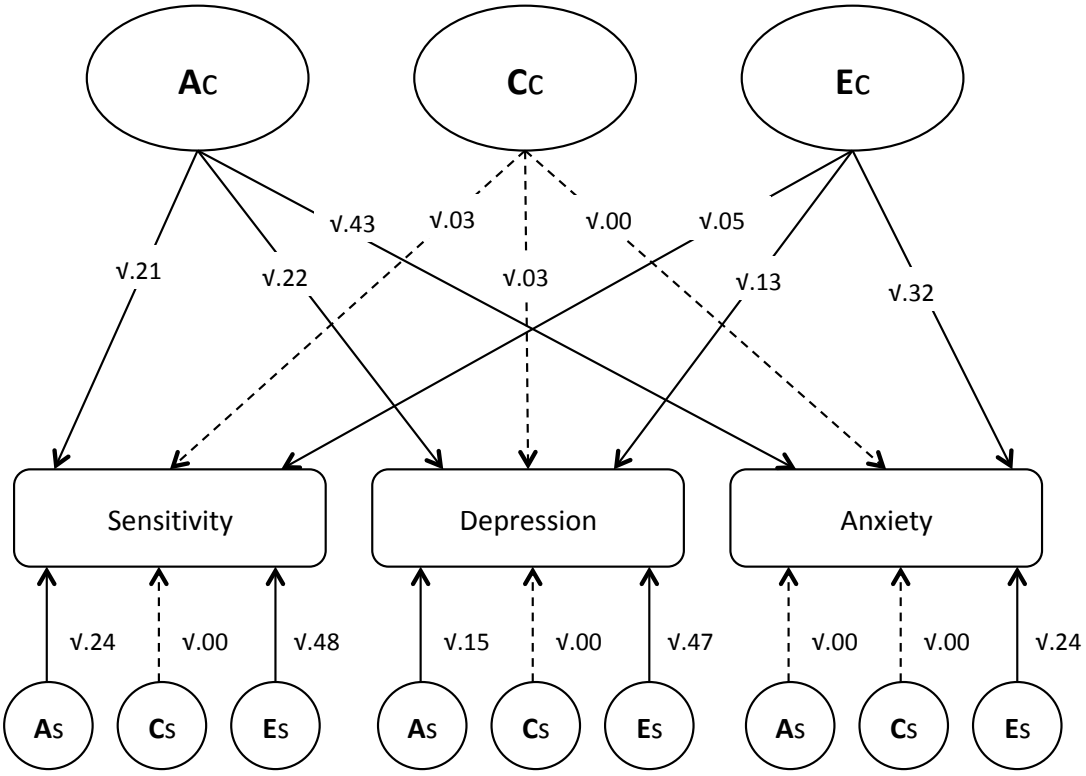


Figure 3.5 Independent pathway model, showing shared and specific genetic and environmental influences on environmental sensitivity and depression and anxiety

Ac= common additive genetic influences; Cc= Common shared environmental influences; Ec= common non-shared environmental influences. As= specific additive genetic influences; Cs= specific shared environmental influences; Es= specific non-shared environmental influences. The paths from common ACE influences to environmental sensitivity and depression and anxiety represent the standardized variance components explained by common ACE influences in each phenotype. The paths from specific ACE influences to environmental sensitivity and and depression and anxiety represent the standardized ACE estimates that are specific to each phenotype. Dashed lines represent non-significant paths.

Table 3.10 Shared and specific ACE influences on HSC and depression and anxiety

	Common ACE influences			Specific ACE Influences			Total - Common ACE	Total- Specific ACE
	Ac	Cc	Ec	As	Cs	Es		
HSC	.21 (.18, .36)	.03 (.00, .14)	.05 (.02, .09)	.24 (.06, .31)	.00 (.00, .12)	.48 (.42, .54)	.29	.72
Depression	.22 (.12, .33)	.03 (.00, .16)	.13 (.07, .21)	.15 (.02, .22)	.00 (.00, .11)	.47 (.39, .34)	.38	.62
Anxiety	.43 (.28, .49)	.00 (.00, .07)	.32 (.21, .55)	.00 (.00, .11)	.00 (.00, .06)	.24 (.02, .34)	.75	.24

Independent pathway model fit summary- HSC and depression and anxiety

Model	Model fit				Fit compared to the saturated model		
	Parameters	-2ll	df	AIC	Δ -2ll	Δ df	*p*
Fully saturated	135	56376.55	8513	39350.55			
Constrained	48	56489.60	8600	39289.60	113.05	87	.03
Independent Pathway	24	56720.10	8624	39472.10	343.55	111	< .001

Ac = common A influences; Cc = common C influences; Ec = common E influences; As = specific A influences; Cs = specific C influences; Es = specific E influences; 95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimate; Total common and specific ACE effects are arrived at by adding up all common ACE and all specific ACE effects, making up total variance =1.

Fully saturated= model with maximum number of parameters describing the data; Constrained = the saturated model constrained to have the same mean and SD across twin and zygosity; −2ll= minus twice the log likelihood; df= degrees of freedom AIC= Akaike's information criterion; Δ -2ll =difference in -2ll value; Δ df= difference in degrees of freedom; *p*= p-value

3.4 Discussion

The current study set out to examine three questions related to individual differences in environmental sensitivity. The first aim was to examine whether individual difference in environmental sensitivity were heritable, as suggested by differential susceptibility theories. The second aim was to examine the genetic architecture of environmental sensitivity as a function of its three components: Ease of Excitation (EOE), Aesthetic Sensitivity (AES) and Low Sensory Threshold (LST). The third aim was to examine the extent to which the commonly reported correlations between environmental sensitivity, the Big Five personality traits, depression and anxiety are due to shared genetic or environmental influences.

With regards to the heritability of environmental sensitivity, the results showed that, in the current sample of adolescent twins from the UK, genetic influences accounted for 47% of the variation in sensitivity, while non-shared environmental influences and measurement error accounted for the remaining 53% of the variance. The results supported differential susceptibility theories' proposition that environmental sensitivity has a genetic basis, whereby genetic variation explained nearly half of the observed individual differences in environmental sensitivity. As well as an ACE model, an ADE model, accounting for non-additive genetic effects, was fitted to the data, the results indicating that additive genetic effects sufficiently explained the heritability of environmental sensitivity. The moderate heritability results of environmental sensitivity, mainly due to additive genetic effects, are in line with previous heritability estimates for common human traits (Polderman et al., 2015). Analyses of sex differences in ACE estimates did not yield significant differences between sexes in the source or extent of variation in environmental sensitivity.

In relation to the genetic architecture of sensitivity as a function of its three components, the results showed that common genetic and environmental influences underlying the three components partly explained the variation in the latent factor of environmental sensitivity. However, as expected, part of the variance in LST and AES was explained by genetic and environmental influences that were specific to these components. These findings suggest that individual differences in environmental sensitivity are a function of two sets of genetic and environmental influences. Whilst the shared genetic factors underlying the three components of sensitivity may reflect variations in general sensitivity to environmental influences, the specific genetic influences on the LST and AES component may determine specific aspects of sensitivity: processes involved in

variations in the threshold and magnitude of reactivity to adverse stimuli (as reflected in LST), and processes involved in attention to detail and reactivity to positive and rewarding stimuli in the environment (as reflected in AES). An implication of this finding is that the presence or absence of specific genetic factors that contribute to different aspects of sensitivity may lead to the existence of different sensitivity types. For example, some sensitive individuals may be predominately reactive to adversity and threats—but not to positive experiences—due to predominately carrying genes that give rise to high EOE and LST, while others are more sensitive to positive—but not negative—aspects of the environment as a function of carrying gene variants associated with AES but not with EOE and LST. This interpretation is supported by current empirical evidence showing distinct associations between the three components of sensitivity and behavioral outcomes. Specifically, while EOE and LST have been associated with sensory-overstimulation (Liss et al., 2008), anxiety, depression (Bakker & Moulding, 2012; Liss et al., 2008), neuroticism and introversion (Sobocko & Zelenski, 2015), AES has been found to correlate with conscientiousness, positive affect and openness (Sobocko & Zelenski, 2015).

With regards to the genetic overlap with personality, depression and anxiety, it was found that high sensitivity was moderately correlated with higher neuroticism, depression and anxiety and lower extraversion, consistent with previous research (e.g. Hofmann & Bitran, 2007; Liss et al., 2008; Smolewska et al., 2006). The results of independent pathway analysis suggested that the majority of the variance in the heritability of environmental sensitivity was explained by the same genetic factors that also influence neuroticism and extraversion (80%), and to a lesser extent depression and anxiety (50%). In contrast, the majority of environmental influences that explain variations in environmental sensitivity are specific to this phenotype, rather than shared with personality traits, though they do overlap to some extent with those underlying variation in anxiety and depression. Overall, these findings suggest that the phenotypic similarities between environmental sensitivity, extraversion and neuroticism were largely due to their underlying shared genetic influences, whereas differences between these traits are predominately influenced by non-shared environmental factors specific to them. The results of depression and anxiety analysis suggest that the phenotypic correlation between them is partly due to shared genetic effects, but also, to a smaller degree, due to similar environmental factors involved in their aetiology.

3.4.1 Strengths and limitations

The current study has several important strengths. These included the use of a twin design to provide a first estimate of heritability of environmental sensitivity in a large, representative sample of twins. Furthermore, this is the first study to examine the shared aetiology of environmental sensitivity with commonly correlated other traits such as personality traits and depression and anxiety. However, the findings have to be considered in light of the following limitations. First, all measures are based on self-report, which may have inflated the observed correlations between the different measures. Examining the correlations using information from various informants would have been able to account for the overestimation. Second, the findings are based on an adolescent sample, which may be affected by the developmental stage of this group. An adult population might have been more suitable, given that personality traits tend to be more stable and reliable in adulthood (Conley, 1984; Hampson & Goldberg, 2006). Third, the subsample with personality measures was smaller than the total sample, which may have prevented reliable detection of smaller effects. Fourth, the general limitations of twin design analysis (Plomin et al., 2013; Rijsdijk & Sham, 2002) also apply to this study, including the difficulty of detecting effects of shared environments, which could have inflated the heritability estimates. Fifth, the internal reliability of the personality and sensitivity measures were relatively low, which could have led to increased measurement error in the current study. However, the personality and environmental sensitivity correlations in the current study were similar to previous research studies, suggesting a good predictive validity of these measures.

3.4.2 Implications and future research

The results of the current study have several implications for future research. Firstly, it was shown that individual differences in the phenotype of environmental sensitivity have a substantial heritable component. The heritability estimates suggest that future molecular genetic studies aimed at identifying the specific genetic variants that contribute to individual differences in environmental sensitivity are warranted. It must be noted, however, that heritability estimates reflect individual differences in a trait in specific population and at the specific time. This is one of the caveats of twin design, since the variance component estimates depend on the specific variance of the population being studied. Notwithstanding this limitation, research findings from twin studies are commonly extended to the general population, regarding twin samples to be representative of non-twin populations. Future studies in different samples using twin

design, or studies estimating heritability using alternative methodologies, such as SNP-based methods, could further test the heritability estimates reported herein. Longitudinal heritability studies would also be informative in examining whether the influence of genetic factors differs across the lifespan. In addition, it was found that environmental factors also play a significant role in shaping environmental sensitivity, emphasizing the need for future research to examine the specific contribution of environmental influences to the development of environmental sensitivity.

Secondly, it was found that environmental sensitivity consists of the combination of three somewhat distinct genetic systems, one that relates to variations in general sensitivity to environmental influences, and others reflected in the specific components that reflect sensitivity to either more negative or more positive aspects of the environment. Future studies should investigate whether these two latter systems, one associated with increased sensitivity to adverse experiences and the other with heightened susceptibility to positive exposures, are the function of specific biological systems.

Finally, it was found that there is a substantial genetic overlap between the genetic influences involved in individual differences in environmental sensitivity and neuroticism, extraversion, depression and anxiety. Future studies on the molecular genetics of environmental sensitivity should be encouraged to examine the genetics of environmental sensitivity as a function of the overlap between these phenotypes.

3.4.3 Conclusions

In conclusion, the reported findings support the theoretical proposition that environmental sensitivity has a significant genetic basis, but that environmental factors play an equally important role. Furthermore, the findings suggest that environmental sensitivity may be best represented as a construct with three genetically distinct underlying systems, one that represents variations in general sensitive to environmental influences, and two others that reflect sensitivity to more positive or negative aspects of environmental exposures. Finally, the substantial genetic overlap between environmental sensitivity and neuroticism, extraversion, depression and anxiety indicates that related genetic influences are involved in these phenotypes.

Chapter 4

Molecular genetics of environmental sensitivity: from candidate gene to genome-wide approaches

4.1 Introduction

The results from **Chapter 3** suggest that general sensitivity to environmental influences, as reflected in the highly sensitive personality trait, is moderately heritable. Quantifying the proportion of variation in a trait attributable to genetic factors is an important first step in establishing the genetic basis of a trait. However, classic heritability studies are not informative as to which genetic variants or biological systems underlie individual differences in sensitivity to environmental influences. The main aim of this chapter is therefore to investigate the molecular genetic factors underlying the detected heritability, by applying various methodologies. The introduction in this chapter is organised into four main parts. The first part briefly explores the propositions related to the molecular genetic factors theorised to be relevant to individual differences in environmental sensitivity. The second part includes a review of genetic findings from research in environmental sensitivity using candidate gene as well as genome-wide approaches. The third part includes a critical evaluation of the research findings in the field. The fourth part includes the aims of this chapter.

4.1.1 The hypothesised genetic-biological basis of environmental sensitivity

As noted in **Chapter 1, Section 1.1.5,** the exact biological mechanism underling variations in environmental sensitivity is unknown; though several potential mechanisms have been proposed. Sensory Processing Sensitivity (Aron & Aron, 1997) proponents have shown that individual differences in environmental sensitivity is associated with brain regions/processes involved in attention and action planning, awareness, integration of sensory information, and empathy (Acevedo, B. P. et al., 2014; Jagiellowicz et al., 2011), therefore implicating the genetic factors that are related to these functional/structural differences. Biological Sensitivity to Context (Boyce & Ellis, 2005; Ellis et al., 2005) proponents have highlighted variations in stress response systems such as autonomic, adrenocortical, or immune reactivity as reflecting individual differences in environmental sensitivity, therefore implicating genetic factors underlying these systems as relevant to the aetiology of environmental sensitivity.

Differential susceptibility hypothesis (Belsky & Pluess, 2009) proponents have mainly emphasized the variations in amygdala reactivity and central nervous systems related to the extent of responsivity/reactivity to environmental stimuli. The authors suggest genetic variations related to individual differences in these systems may reflect individual differences in environmental sensitivity, specially nominating dopaminergic

and serotoninergic system genes based on their review of the genetic literature that identifies several variants from these systems as environmental sensitivity candidates.

The "neurosensitivity" hypothesis, Belsky and Pluess (2013a) integrates these different suggested mechanisms, by proposing that heightened environmental sensitivity may be the function of a generally more sensitive central nervous system, reflected in various biological, physiological and psychological domains. Therefore, the genetic and environmental factors that influence these various structural and physiological functions of brain and the central nervous system, would be implicated in individual differences in general environmental sensitivity.

With regards to a genetic model of sensitivity, Moore and Depue (2016) provided a detailed theoretical biological model of environmental sensitivity based on their review of the environmental sensitivity candidate gene literature and other functional genetic studies of these variants in human and animal models. They propose an interactive biological-genetic model for the involvement of several neurotransmission (dopamine, GBA, norepinephrine, serotonin) and neuropeptide (opiates, oxytocin, corticotrophin-releasing hormone) gene systems involved in biological reactivity to environmental influences. They suggest that the biological systems that underlie reward sensitivity, depth and breadth of processing, neuronal learning and response inhibition, all play an important role in the development of individual tendencies for higher or lower biological reactivity to environmental stimuli, and the manifestation of a behavioural phenotype of general high or low sensitivity. Though their proposed interactive genetic-biological model has yet to be cexamined empirically, it does provide a potential explanation for the role of dopaminergic and serotoninergic genes in the aetiology of environmental sensitivity.

Indeed, research evidence does support the involvement of these systems. For example, the serotonin-transporter-linked polymorphic region (*5-HTTLPR*), a commonly studied genetic variation in the Solute Carrier Family 6 Member 4 *(SLC6A4)* gene, has been associated with cognitive performance (Homberg & Lesch, 2011), variations in amygdala reactivity (Munafo et al., 2008), and also found to moderate the impact of socio-economic status on central nervous serotonergic responsivity (Manuck, Flory, Ferrell, & Muldoon, 2004). Variants in the Dopamine Receptor D4 (*DRD4*) and Dopamine Receptor D2 (*DRD2*), two other sensitivity genes from the dopaminergic system, have been found to moderate the effects of parental intervention on toddler's salivary cortisol levels (Bakermans-Kranenburg et al., 2008), family stress on audio-

spatial ability (Berman & Noble, 1997), and maternal sensitivity on respiratory sinus arrhythmia – a measure of stress reactivity (Propper et al., 2008). It must be noted that despite supportive evidence, the function of these sensitivity genes is not unique to the suggested environmental sensitivity brain structures/functions or bio-physiological processes, therefore their specific contribution to variations in general environmental sensitivity remains unknown.

4.1.2 Review of genetic association studies of environmental sensitivity

4.1.2.1 Candidate gene research

Single Nucleotide Polymorphisms (SNP) or Variable Number Tandem Repeats (VNTRs) are two of the most commonly examined types of variation in the human genome in genetic associations studies. In a candidate gene association study, the first step is to identify a gene and variant within that gene that is proposed to be involved in the aetiology of the examined phenotype. Once the candidate gene variant has been selected according to its known or hypothesised biological relevance, the sample is split into groups depending on their genotype (i.e. homozygote for common allele, homozygote for rare allele or heterozygote) and examined for their association with the phenotype/disorder. If genetic variation is significantly associated with the risk for disease/trait, the genetic variant is implicated as a risk factor/biologically relevant for the trait. This type of association study makes an important assumption: that the selected genetic variant has functional consequences in the biological underpinning of the trait. Another approach, Gene x Environment interaction (GxE), makes the same assumption about the biological relevance of the selected candidate gene for the trait, but hypothesises that genetic variation by itself may not exert a significant effect on the trait, rather its effect is through its interaction with an environmental (risk) factor. If the impact of the environmental factor (e.g. stressful life events) on the trait (e.g. depressive symptoms) is found to be dependent on the genotype (e.g. a moderating effect of genotype), the genetic variant is considered as a risk factor for, and relevant to the aetiology of the examined trait. While much of the early GxE studies have been conducted with single SNPs or VNTRs, recent candidate approaches have considered the cumulative effect of several candidate genetic variants. In these approaches, a total score is created for each individual based on the number of risk alleles present. Standard GxE models are then used to examine the extent to which this score moderates the effects of a measured environmental factor on a given outcome.

As detailed in the **Chapter 1,** much of the evidence for the genetic basis of environmental sensitivity, prior to establishing its heritability in the previous chapter, comes from GxE studies. The guiding principle for identifying environmental sensitivity genes in such studies is their *pattern of interaction* with the environmental factor (Belsky & Pluess, 2009). Under the differential susceptibility framework, the environmental factor is expected to be on a continuum ranging from negative/risk to positive/protective. Genetic moderation action is proposed to be consistent with a cross-over interaction, where the variant moderates the outcome for worse at the risky end of the environmental factor and for better in the positive context. In addition to the above condition, a more stringent benchmark requires that: 1) the slope for the highly sensitive group is significantly different from zero; 2) the slope for the highly sensitive group is significantly steeper than the slope for the less sensitive group; and 3) that there are no genotype - environmental correlations as they reflect passive and active effects of genes on environment and dual-risk for the outcome rather than genetic sensitivity (Belsky, Bakermans-Kranenburg, et al., 2007). Presence of such an interaction pattern typically identifies the studied gene as a *sensitivity gene* rather than mere vulnerability gene, and the risk allele as a *sensitivity allele*. Other approaches have since been developed that include competitive model testing (Widaman et al., 2012) or regions of significance analysis (Roisman et al., 2012), that present yet more stringent criteria for identifying crossover interaction patterns. The next section includes an overview of these nominated sensitivity genes/genetic variants from differential susceptibility-influenced studies and empirical evidence for some of the most consistent findings from candidate genes studied so far.

4.1.2.2 Environmental sensitivity candidate genes

In their seminal paper on differential susceptibility hypothesis, Belsky and Pluess (2009) identified commonly studied variants in 8 genes from previous GxE studies (*SCL6A4*, *DRD2, DRD4*, Monoamine Oxidase A (*MAOA*), Catechol-*O*-methyltransferase *(COMT)*, dopamine active transporter 1 gene (*DAT1),* 5-Hydroxytryptamine Receptor 2A (*HTR2A),* Tryptophan hydroxylase 1 *(TPH1*)) as environmental sensitivity candidate genes, based on their interaction patterns with environmental factors. These studies included a wide range of environmental factors and outcomes such as maternal nurturance and depression, birth weight and educational achievement, parenting practices and externalising behaviours, childhood emotional abuse and anxiety sensitivity, and parental divorce and adult relationship stability. They

have noted that the impact of these environmental influences is dependent on the genotype and that the interaction pattern is consistent with a cross over interaction, whereby a specific variant is associated with increased risk of negative outcomes in adverse contexts, but also less risk in the absence of environmental risk factor/in positive context. An updated review of the literature by Belsky and Pluess (2013a), nominated several additional environmental sensitivity candidate genes based on emerging evidence, suggesting variations in Brain-derived neurotrophic factor (*BDNF),* Oxytocin Receptor *(OXTR),* and FK506 Binding Protein 5 *(FKBP5)* genes may moderate the impact of environmental influences consistent with the differential susceptibly hypothesis. More recent studies in the field have moved on from examining single gene variants, instead examining the effects of multiple sensitivity genes and how their combined or interactive effects moderate the impact of experiences on outcomes. For example, Drury et al. (2012) reported on the cumulative effects of the Val66Met polymorphism in *BDNF* and *5-HTTLPR* short allele on response to a foster-care intervention study. Specifically, they found that children with the highest number of sensitivity alleles across both loci experienced the greatest decrease in indiscriminate social behaviour when put into foster care, and the greatest increase in such behaviour if they remained institutionalised. Several more candidate sensitivity genes have since been identified in GxE research according to their crossover interaction pattern. **Table 4.1a and 4.1b** show a list of the older and also newly identified candidate environmental sensitivity genes since the Belsky and Pluess (2009) paper. Though this is not a systematic review of the literature in the field, nor a comment on the strength of the studies included, these studies include the majority of GxE studies that have been published between 2009 and 2017, and in which the interaction pattern is consistent with a differential susceptibility model. The sample in all of these studies include more than 100 individuals, with findings having been replicated in at least one other study.

Table 4.1a Example of candidate environmental sensitivity genes identified from studies showing the GxE interaction pattern consistent with differential susceptibility theories *

Authors (year)	Environmental variable	Outcome measure	Sample
	SLC6A4 (*5-HTTLPR* VNTR)		
Benjet, Thompson, and Gotlib (2010)	Relational peer victimization	Mental health	Adolescents (*N*=303)
Hammen, Brennan, Keenan-Miller, Hazel, and Najman (2010)	Family discord	Depressive symptoms	Adults (*N*=346)
Hayden et al. (2010)	Positive emotionality	Negative emotionality	Children (*N*=413)
Jacobs et al. (2011)	Maternal depressive history	Errors in face-emotion labelling	Adolescents (*N*=123)
Brody et al. (2011)	Perceived discrimination	Conduct problems	Adolescents (*N*=461)
Mileva-Seitz et al. (2011)	Mother's early life experiences	Maternal behaviour and attitudes	Adults (*N*=204)
Carver, Johnson, Joormann, Kim, and Nam (2011)	Childhood adversity	Impulsivity	Adolescents (*N*=303)
Hankin et al. (2011)	Idiographic stressors	Depression symptoms	Children (*N*=220)
Verschoor and Markus (2011)	Exam stress	Mood, Perceived stress	Adolescents (*N*=771)
Fox, Zougkou, Ridgewell, and Garner (2011)	Attention bias modification training	Change in attentional bias	Adults (*N*=116)
Xie, Kranzler, Farrer, and Gelernter (2012)	Childhood adversity	PTSD	Adults (*N*=5178)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
Wald, Degnan, Gorodetsky, and et al. (2013)	Attentional bias	PTSD	Adults (*N*=1085)
Bogdan, Williamson, and Hariri (2012)	Stressful life events	Depressive symptoms	Children (*N*=234)
Haase et al. (2013)	Emotional behaviour	Marital satisfaction	Adults (*N*=125)
Davies and Cicchetti (2014)	Maternal unresponsiveness	Externalizing problems	Children (*N*=201)
Beach, Dogan, Brody, and Philibert (2014)	Socioeconomic status	Methylation	Adolescents (*N*=338)
Babineau et al. (2015)	Prenatal depression	Behavioural dysregulation	Children (*N*=213)
VanZomeren-Dohm, Pitula, Koss, Thomas, and Gunnar (2015)	Institutional rearing & peer victimization	Depressive symptoms	Children (*N*=489)
Brett et al. (2015)	Foster Care	Externalising behaviour	Children (*N*=102)
Bouvette-Turcot et al. (2015)	Maternal childhood adversity	Negative emotionality	Children (*N*=154)
Sumner, McLaughlin, Walsh, Sheridan, and Koenen (2015)	Maternal care	Stress reactivity	Adolescents (*N*=113)
Lei et al. (2016)	Relationship satisfaction	Physiological stress response (Thyroid function)	Adults (*N*=270)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
		APOE	
Kring et al. (2010)	Caregiver stress	Triglyceride in blood	Adolescents (*N*=248)
Taylor et al. (2011)	Flying experience	Flight simulator performance	Adults (*N*=139)
		BDNF	
Hayden et al. (2010)	Parental depression	Negative emotionality	Children (*N*=413)
Suzuki et al. (2011)	Parenting	Harm avoidance	Adults (*N*=710)
Gunnar et al. (2012)	Institutional care	Attention problems	Adolescents (*N*=612)
Chen, Li, and McGue (2012)	Stressful life events	Depressive symptoms	Adolescents (*N*=780)
Chen et al. (2015)	Antenatal maternal anxiety	Neonatal DNA methylation	Children (*N*=780)
Ward et al. (2015)	Cognitive Reserve	Executive Function	Adults (*N*=433)
Zhang, L. et al. (2016)	Maternal parenting	Depressive symptoms	Adolescents (*N*=780)
Miu et al.	Child maltreatment	Reappraisal ability	Adults (*N*=254)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
		COMT	
Brennan et al. (2011)	Prenatal smoking	Aggressive behaviour	Adolescents (*N*=430)
Laucht et al. (2012)	Perceived parenting behaviour	Alcohol use	Adolescents (*N*=285)
Kok et al. (2013)	Parenting	Compliance	Children (*N*=613)
Baumann et al. (2013)	Childhood Trauma	Anxiety sensitivity	Adults (*N*=782)
Hygen et al. (2015)	Serious life events	Aggression	Children (*N*=704)
		DAT1/SLC6A3	
Lee et al. (2010)	Child disruptive behaviour	Negative parenting	Adults (*N*=127)
Lahey et al. (2011)	Parenting	Conduct disorder	Children (*N*=310)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
		DRD2	
van Roekel, Goossens, Scholte, Engels, and Verhagen (2011)	Parental support	Loneliness	Adolescents (*N*=307)
(Lee, Brooks-Gunn, McLanahan, Notterman, & Garfinkel, 2013)	Macroeconomic conditions	Harsh parenting	Adults (*N*=2612)
Chhangur et al. (2015)	Parental Support	Delinquent behaviour	Adolescents (*N*=308)
Zhang et al. (2015)	Negative Parenting	Depressive symptoms	Adolescents (*N*=1026)
		DRD4	
Sweitzer et al. (2012)	SES	Impulsivity	Adults (*N*=546)
Beach et al. (2012)	Contextual stressors	Negative arousal	Children (*N*=345)
Berry et al. (2013)	Maternal sensitivity	Attention problems	Children (*N*=711)
Kretschmer, Dijkstra, Ormel, Verhulst, and Veenstra (2013); Zohsel et al. (2014)	Prenatal stress	Externalizing problems	Children (*N*=308)
Brody et al. (2014)	Intervention	Substance use	Adolescents (*N*=502)
Cho and Kogan (2016)	Community disadvantage	Risk behaviour	Adolescents (*N*=309)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
		ESR1	
Hartman, Widaman, and Belsky (2015)	Maternal Sensitivity	Onset of menarche	Adolescents (*N*=210)
Manuck, Craig, Flory, Halder, and Ferrell (2011)	Family environment	Menarche	Adults (*N*=455)
		FKBP5	
Xie et al. (2010)	Childhood Adversity	PTSD	Adults (*N*=2427)
Zimmermann et al. (2011)	Adverse life event	Major depression	Adults (*N*=884)
Bevilacqua et al. (2012)	Childhood Trauma	Aggressive behaviour	Adults (*N*=583)
White (2012)	Emotional neglect	Amygdala reactivity	Adolescents (*N*=139)
Klengel et al. (2013)	Childhood maltreatment	PTSD	Adults (*N*=519)
VanZomeren-Dohm et al. (2015)	Peer victimisation	Depressive symptoms	Children (*N*=489)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
		GABRA2	
Enoch, M.-A. et al. (2010)	Childhood trauma	Addiction vulnerability	Adults (*N*=577)
Trucco, Villafuerte, Burmeister, and Zucker (2017)	Peer affiliation	Externalising behaviour	Adolescents (*N*=504)
Villafuerte, Trucco, Heitzeg, Burmeister, and Zucker (2014)	Peer delinquency	Externalising problems	Adolescents (*N*=244)
		HTR2A	
Salo, Jokela, Lehtimaki, and Keltikangas-Jarvinen (2011)	Childhood maternal nurturance	Social attachment in adulthood	Adolescents (*N*=1070)
Fraley, Roisman, Booth-LaForce, Owen, and Holland (2013)	Maternal Sensitivity	Avoidance (Attachment)	Adolescents (*N*=503)
		MAOA	
Enoch, Steer, Newman, Gibson, and Goldman (2010)	Stressful life events	Behvarioural disinhibition	Children (*N*=7500)
Baumann et al. (2013); Wakschlag et al. (2010)	Prenatal exposure to cigarettes	Antisocial behaviour	Adolescents (*N*=176)
Baumann et al. (2013)	Childhood Trauma	Anxiety sensitivity	Adults (*N*=782)

Table 4.1a Continued

Authors (year)	Environmental variable	Outcome measure	Sample
	OXTR		
Johansson et al. (2012)	Alcohol use	Aggression	Adults (*N*=116)
Hostinar, Cicchetti, and Rogosch (2014)	Childhood maltreatment	Social support & internalising problems	Adolescents (*N*=425)
Hammen, Bower, and Cole (2015)	Family quality	Borderline personality symptoms	Adolescents (*N*=385)
Dannlowski et al. (2016)	Childhood maltreatment	Ventral striatum volume	Adults (*N*=309)

*Includes only studies with sample sizes of more than 100 individuals and with genes having been replicated in at least one other study

Table 4.1b Example of studies using multiple candidate environmental sensitivity genes, showing candidate polygenic score xE interaction pattern consistent with differential susceptibility theories *

Sensitivity genes	Authors (year)	Environmental variable	Outcome measure	Sample
COMT,BDNF	Simons et al. (2009)	Daily stress	Paranoia experiences	Adults (*N*=621)
COMT, 5-HTTLPR	Nijmeijer et al. (2010)	Maternal prenatal smoking	ADHD	Children (*N*=646)
5-HTTLPR, DRD4	Simons et al. (2011)	Social environment	Aggression	Adolescents (*N*=867)
DAT1, DRD2, DRD4, 5-HTTLPR, MAOA	Belsky and Beaver (2011)	Parenting	Self-regulation	Adolescents (*N*=1586)
BDNF, CREB1	Juhasz et al. (2011)	Childhood adversity	Depressive symptoms	Adults (*N*=1570)
5-HTTLPR, STin2	Mitchell et al. (2011)	SES	Postpartum depression	Adults (*N*=1206)
5-HTTLPR, BDNF	Clasen, Wells, Knopik, McGeary, and Beevers (2011)	Life Stress	Rumination	Adolescents (*N*=273)
5-HTTLPR, CRHR1	Cicchetti, Rogosch, and Oshri (2011)	Child maltreatment	Internalizing problems	Children (*N*=493)
5-HTTLPR, TPH1, MAOA	Cicchetti et al. (2012)	Child maltreatment	Antisocial behaviour	Children (*N*=627)
5-HTTLPR, MAOA	Priess-Groben and Hyde (2013)	Negative life events	Depression	Adolescents (*N*=309)

Table 4.1b Continued

Sensitivity genes	Authors (year)	Environmental variable	Outcome measure	Sample
5-HTTLPR, CRHR1, OXTR, DRD4	Cicchetti and Rogosch (2012)	Child maltreatment	Resilience	Children (*N*=595)
DRD2, DRD4, COMT	Nederhof, Belsky, Ormel, and Oldehinkel (2012)	Divorce	Externalizing behaviour problems	Adolescents (*N*=1134)
5-HTTLPR, OXTR	Sturge-Apple, Cicchetti, Davies, and Suor (2012)	Parental Conflict	Maternal sensitivity & harsh parenting	Adults (*N*=201)
GABRA1, GABRA2 DRD2, DRD4, ANKKI	Brody, Chen, and Beach (2013)	Prevention Program	Alcohol use	Adolescents (*N*=900)
5-HTTLPR, DRD4, DAT1, COMT	Masarik et al. (2014)	Parent-child interaction	Behaviour in romantic relationship	Adults (*N*=352)
BDNF, COMT, SIRT1	Brett et al. (2014)	Institutional care	Neurodevelopmental outcomes	Children (*N*=193)
OXTR, FK506	Cicchetti, Rogosch, Hecht, Crick, and Hetzel (2014)	Childhood maltreatment	Borderline personality	Children (*N*=1051)
TPH2, HTR1A, HTR2A	Pearson, McGeary, and Beevers (2014)	Childhood maltreatment	Behavioural approach system (BAS)	Adults (*N*=236)
BDNF, FKBP05, NET, CHRH1	Cicchetti and Rogosch (2014)	Childhood maltreatment	Depressive & internalising symptoms	Children (*N*=1096)
5-HTTLPR, BDNF	Dalton, Hammen, Najman, and Brennan (2014)	Family environment	Depressive symptoms	Adolescents (*N*=363)

Table 4.1b Continued

Sensitivity genes	Authors (year)	Environmental variable	Outcome measure	Sample
DRD2, DAT1	Ludmer et al. (2015)	Strange situation procedure	Cortisol reactivity	Infants (*N*=314)
HTR1A, *HTR2A*, *HTR2C*, *TPH2*	Vrshek-Schallhorn et al. (2015)	Life events	Depression	Adults (*N*=387)
MAOA, COMT	Zhang, Cao, Wang, Ji, and Cao (2016)	Parenting	Reactive aggression	Adolescents (*N*=1399)
5-HTTLPR, DRD4	Green et al. (2017)	Prenatal maternal depression	Negative emotionality	Children (*N*=179)
5-HTTLPR, DAT1, DRD4	Richards et al. (2016)	Maternal warmth	Neural reward sensitivity	Adolescents (*N*=443)

*Includes only studies with sample sizes of more than 100 individuals

Though most of the research adhering to the differential susceptibility framework has found support for these candidates as sensitivity genes, there are some others who have found an interaction pattern consistent with diathesis-stress model, inferring only risk, rather than general sensitivity (Brody et al., 2012; Kochanska et al., 2011). Meta-analysis of the GxE studies however has shown some candidate gene findings to be robust. For Example, two meta-analyses found consistent effects for *5-HTTLPR* (Van IJzendoorn, M., Belsky, J., & Bakermans-Kranenburg, M., 2012) and *DRD4 7* repeat (Bakermans-Kranenburg & van IJzendoorn, 2011), showing the moderating effects of these variants is consistent with differential susceptibility theories rather than diathesis stress model, in response to a wide range of environmental experiences across childhood and adolescence.

5-HTTLPR is a genetic polymorphism in the promoter region of the serotonin transporter gene *(SLC6A4)* (Heils et al., 1995). The protein product of this gene (5-HTT) is expressed in the central and peripheral nervous systems and plays a key role in transporting the neurotransmitter serotonin from synapses to presynaptic neurons. The polymorphism consists of a long (l-allele) and a short (s-allele) variant, based on the insertion or deletion of 44 base pairs close to the beginning of the gene's transcription site. The S-allele has been associated with lower and the l-allele with higher levels of serotonin transporter mRNA transcription (Lesch, Bengel, Heils, & Sabol, 1996), and the short repeat variant (s-allele) has been identified as the sensitivity allele since it often shows less negative outcomes in the absence of adversity/presence of protective factors, but more negative outcomes in the context of adversity. For example, studies with *5-HTTLPR* have found it moderates *for better and for worse*, the impact of maternal responsiveness on children's moral development (Kochanska et al., 2011), the effect of parenting practices on children's positive affect (Hankin et al., 2011), perceived racial discrimination on conduct problems and of child maltreatment on antisocial behavior (Cicchetti et al., 2012). The *5-HTTLPR* S-allele has also been associated with higher neuroticism in the context of negative life events, but also lower levels of neuroticism and higher life satisfaction in the context of positive life events (Kuepper et al., 2012; Pluess, Belsky, Way, & Taylor, 2010). In one of the largest candidate gene studies (N=1,206), Mitchell et al. (2011) studied the effects of *5-HTTLPR* and Serotonin Transporter Intronic VNTR Enhancer (*STin2)*, another serotoninergic system VNTR located in the intron 2 region of the *SLC6A4* gene which is believed to cooperate with the regulatory function of *5-HTTLPR*. This study

investigated the combined effects of these genes on moderating the impact of SES on postpartum depression in the first year after birth. They found that some mothers were more genetically sensitive to their environments (higher number of 12 repeat for *STin2* and s-allele for *5-HTTLPR*) resulting in a crossover of risks of postpartum depression in the context of high and low SES for these genetically sensitive individuals.

DRD4 encodes the D4 subtype of the dopamine receptor, which is responsible for neuronal signaling in the mesolimbic system of the brain, an area of the brain that regulates emotion and complex behavior. This gene contains a polymorphic number (2-10 copies) of tandem 48 repeats. And the 7 repeat polymorphism has been associated with decreased efficiency in dopamine reception (D'Souza & Craig, 2006), and consistently identified as a sensitivity allele. For example, Berry et al. (2013) found that the *DRD4* 7 repeat was associated with higher inattention in the context of insensitive early maternal care, but also with lower levels of inattention in the context of more sensitive maternal care. Similar interaction patterns have been observed regarding the effects of quality of child-care on the development of social competence (Belsky & Pluess, 2013b), effects of parenting on prosocial behavior (Knafo et al., 2011), effects of positive changes in parenting practices on children's externalizing behavior (Bakermans-Kranenburg et al., 2008), and of childhood adversity on emerging adulthood alcohol dependence (Park, Sher, Todorov, & Heath, 2011). In studies on substance use in adolescents, the results have shown that the effects of intervention programs for substance use was greater for 7 repeat carriers, even though this genotype was associated with higher risk of substance use in the absence of intervention (Beach, Brody, Lei, & Philibert, 2010; Brody et al., 2014).

DAT1 is another gene in the dopaminergic system that has been studied as a single candidate or in combination with *DRD4* and consistently found to be associated with differential susceptibility to environmental influences. The product of this gene is a membrane-spanning protein that mediates the reuptake of dopamine from the synapse. *DAT1* is the primary regulator of dopamine neurotransmission and is expressed in the central nervous system, primarily in brain areas that make up the dopaminergic circuits (e.g. striatum and nucleus accumbens). In one of the earliest larger studies of *DAT1*, Sonuga-Barke et al. (2009) examined whether the impact of maternal expression of positive emotions (a protective factor) on conduct disorder and emotional problems in a sample of 5 to 17 year olds (N= 728), depended on children's *DAT1* and *DRD4* genotype. They found that the protective effects of maternal

expression of positive emotions on reduction of emotional and conduct problems was evident only for those with 9 repeat variants of the *DAT1* (sensitivity allele), whereas those without the sensitivity allele did not show alterations in response to this positive environmental influence. In other more recent studies, *DAT1* has been found to moderate the influence of positive and negative parenting practices on conduct disorder (Lahey et al., 2011), and the impact of parents behavioural training on children's attention deficit hyperactivity disorder (ADHD) symptoms (van den Hoofdakker et al., 2012), consistent with differential susceptibility pattern of for better and for worse interaction.

MAOA is another widely studied sensitivity gene. Although there is currently no meta-analysis of *MAOA* studies to show that its interaction pattern is consistent with differential susceptibility theories, the low-activity allele has been frequently found to reflect a sensitivity genetic variant, usually in larger samples that is typical of studies in this field. *MAOA* gene is located on the X-chromosome (Levy et al., 1989) and encodes mitochondrial enzymes that are involved in degrading of other amine neurotransmitters such as dopamine, serotonin and norepinephrine (Shih, Chen, & Ridd, 1999). A functional VNTR (2, 3, 3.5, 4 or 5 repeats) exists in the promoter region of the gene (Sabol, Hu, & Hamer, 1998), with short (3 repeat) versus long (4 repeat) associated with low versus high *MAOA* expression, respectively, and therefore higher or lower levels of amine neurotransmitters (Deckert et al., 1999; Sabol et al., 1998). The low-activity *MAOA* alleles have been nominated as sensitivity allele (Belsky & Pluess, 2009), following studies showing that, for example, low-*MAOA*-activity allele infers higher risk of conduct disorder in childhood and antisocial behavior in adulthood in the context of childhood maltreatment, but lower risks for these problem behaviours in the absence of childhood maltreatment (Caspi et al., 2002; Foley et al., 2004; Kim-Cohen et al., 2006). Much of the subsequent studies on *MAOA* have been conducted on antisocial behavior or its correlates such as aggression and impulsivity and ADHD. In one of the largest of *MAOA* studies, Enoch, M. A. et al. (2010) tested the impact of family adversity from pre-birth to age 3 years and stressful life events from 6 months to 7 years on hyperactivity and behavioural problems in 7,500 girls and boys. Although the authors did not set out to test the differential susceptibility hypothesis, the interaction pattern indicated *MAOA* low activity as the sensitivity allele, whereby it increased the risk of hyperactivity in both boys and girls at ages 4 and 7 in response to stressful life events in childhood. However, low activity *MAOA* was also associated with lower risk

at the less risky end of environmental index, compared to those with the high activity allele. In another study with 782 adults, *MAOA* low activity allele was found to function in similar differential susceptibility manner when authors tested the impact of childhood trauma on anxiety proneness (Baumann et al., 2013).

4.1.2.3 Genome-wide studies of environmental sensitivity

Considering the limitations of candidate gene studies, along with the availability and affordability of genome-wide genotyping platforms, research in behavioural genetics transitioned into a Genome-wide era in the early 2000s. The fundamental difference between candidate-gene approaches and genome-wide approaches lies in the requirement for a-priori hypothesis for the candidate genes approaches versus the hypothesis-free nature of genome-wide approaches. Instead of examining one or a small selection of SNPs as in the candidate approach, genome-wide approaches examine the associations between several thousand variations from across the genome and the trait of interest. This approach makes several assumptions, such as assuming that the examined trait is to some extent heritable, and that the genotyping array either directly assays, or is in linkage disequilibrium with all of the variants that explain the heritability. The heritability assumption may be easily met, since years of behavioural genetic research have shown almost all human traits are moderately heritable (Polderman et al., 2015). While other DNA structural variations such as rare variants, Copy Number variants (CNVs) or insertions and deletions (Indels) have been studied in GWAS, most studies of common traits are conducted on common SNPs, in line with evidence that common SNPs explain a substantial amount of additive genetic effects in common traits/disorder (Visscher et al., 2017)

One of the first of such approaches is Genome-wide association study (GWAS), where commonly the association between a trait and, for example, over 500,000 SNPs is tested in a series of t-tests. The SNPs most strongly associated with the trait/outcome, as inferred by the lowest p-value, are considered to play an important role in the aetiology of the trait. However, acknowledgement of the limitations inherent within the GWAS approach, such as stringent correction for multiple testing, and requirements for large sample sizes to ensure sufficient power to detect small effects of single variants on complex traits, have led to the development of other approaches such as polygenic risk scores. Polygenic approaches incorporate GWAS as the first step for estimating the extent of association between each SNP and the trait in a discovery sample, followed by

construction of a polygenic risk score for each individual in an independent target sample, by summing the associated alleles weighted by their effect size (e.g. β-coefficient). The polygenic scores are then used to predict variation in the trait in the target sample. The polygenic score therefore reflects the additive genetic risk for a trait. This approach considers that the genetic basis of common traits is polygenic and that even SNPs with small effects on the trait may be involved in its aetiology through additive genetic effects (Visscher et al., 2017). Another application of polygenic scores, which we call *cross-trait polygenic score*, incorporates the same methodology, but examines the shared genetic influences between different traits, due to pleiotropic effects, a situation in which a single variant influences multiple phenotypes (Hodgkin, 1998). This approach examines this effect by testing whether the variation in a target phenotype (e.g. depression) is explained by the polygenic score constructed based on GWAS summary statistics of another trait (e.g. neuroticism). Shared genetic effects have been commonly observed in genetic studies of human disorders and traits (Bulik-Sullivan et al., 2015; Cross-Disorder Group of the Psychiatric Genomics, 2013)

To date, there has been no GWAS of an environmental sensitivity phenotype. However, there is one study that has used a genome-wide approach to study environmental sensitivity under the differential susceptibility framework. In this study, Keers et al. (2016) devised a novel approach to capture variants that infer variable sensitivity to environmental influences, taking advantage of the genetic relatedness of MZ twin pairs (N= 1,026). Because MZ twin pairs are genetically identical and share the same environments, their discordance on any trait/outcome is considered to be the result of environmental influences that are unique to each twin. Keers et al. (2016) used this principle to propose that greater intra-pair variability on an outcome could be the result of the increased sensitivity to non-shared environmental influences. Using this approach, they created polygenic score of environmental sensitivity from the MZ difference scores on emotional problems and tested the score as a moderator of parenting on emotional problems in an independent sample of 1,400 children. They found that this polygenic score of sensitivity to environmental influences moderated the effects of parenting in a manner consistent with differential susceptibility theories. Specifically, for individuals with a low genetic sensitivity score, parenting did not exert a significant effect on their emotional problems. In contrast, higher genetic sensitivity scores were associated with higher emotional problems in the context of negative parenting, but also decreased emotional problems in the context of positive parenting.

The results therefore suggest that their polygenic score may reflect individual differences in environmental sensitivity.

4.1.3 Critical evaluation of research findings

While genetic research on environmental sensitivity has been instrumental in providing initial support for the hypothesised genetic basis of environmental sensitivity, they do have limitations. Firstly, as noted earlier, all current studies related to genetics of environmental sensitivity are conducted using candidate gene methodology, an approach that has been the focus of intense scrutiny in the last decade. This is largely because, the primary requirement of a candidate gene approach is selection of candidate genes based on a biological hypothesis, however knowledge regarding the specific biological mechanisms underlying complex psychological traits, including environmental sensitivity, remains rather limited. For this reason, the risk of selecting inappropriate candidates is high. However, due to the documented publication bias for significant novel results over null or negative results (Bosker et al., 2011; Collins, Kim, Sklar, O'Donovan, & Sullivan, 2012), the candidate gene literature would give the impression that candidate gene studies are a more robust method for detecting associations than is the reality. This is an important limitation especially for candidate gene research in environmental sensitivity, whereby the initial candidate genes were identified based on their observed interaction pattern with environmental factors, rather than from biologically established/hypothesised mechanisms underlying the trait as a first step. Importantly, the current hypotheses regarding its biological/genetic basis have been built partly based on post-hoc interpretation of candidate gene findings themselves (e.g. see Belsky & Pluess, 2009). This circular reasoning makes the rational for selection of genes in the candidate gene studies of environmental sensitivity even more lacking. Despite this main limitation of candidate gene approaches, they are still worthwhile in establishing associations between functional genetic variants and a trait, especially if there is strong evidence from sufficiently powered studies, and the findings are robust in meta-analysis. GWAS would provide an alternative approach by facilitating the exploration of the genetic influences on individual differences in environmental sensitivity without an a-priori hypothesis, and could be complimentary to candidate gene approach by validating the candidate gene findings or nominating novel candidates for further investigation; an approach that is yet to be employed in research on environmental sensitivity.

Second, and related to the previous limitation, is the evidence suggesting that the genetic architecture of common traits are polygenic and influenced by many thousands of gene variants, each of very small effect rather than by a few variants of large effect (Culverhouse et al., 2017; Visscher et al., 2017). While recent GxE research in environmental sensitivity has attempted to partly address this point, by including several, rather than one candidate gene in their studies, these commonly include less than 10 variants of the potential 10 million variants in human genome. Genome-wide polygenic scores, capturing additive genetic influences on individual differences on a trait, can address this limitation, though there are currently no such studies on environmental sensitivity. In addition, all studies in the field have so far only examined DNA sequence variation at the SNP level. Other approaches attempt to investigate the genetic basis of traits at the level of genes or genetic pathways, rather than SNPs. In gene-based approaches, the unit of association is a gene rather than a SNP, with the idea that gene-level variations better summarise the functional genetic consequences for a trait than its constituent parts (e.g. SNPs) (Neale & Sham, 2004). Pathway models emphasise the biological relevance of genes in a trait, by looking at the association between a trait and a network of genes (e.g. 200 genes) that are deemed to play an important role in specific biological pathways (e.g. serotoninergic) in human functioning (e.g. synaptic activity). These alternative analytical approaches offer a different prospective in studying individual differences in environmental sensitivity, an important gap in research that is yet to be explored.

Finally, apart from the methodological limitations noted so far, there is a caveat in applying the findings from the GxE studies in the field to examining the genetic variants related to individual differences in a phenotype of environmental sensitivity. Specifically, while candidate genetic variants such as *5-HTTLPR*, *DRD4*, and *MAOA* seem to reflect differential sensitivity to environmental influences through their moderating action (operational effects), they may not be as important or relevant to aetiology of the phenotype of environmental sensitivity and its formation over time (trait effects). This is because, GxE studies examine the response to *specific events* for *specific outcomes*, whereas the phenotype of environmental sensitivity (e.g. highly sensitive personality trait) reflects *general tendencies* in response to all environmental stimuli. It is therefore not a forgone conclusion that the genetic variants identified though GxE studies perpetuate the same response in other environments and for other outcomes (i.e. reflect general sensitivity), until there is an empirical test of their

association with variations in the phenotype of environmental sensitivity. To date, only one study (Chen et al., 2011) has examined the genetic basis of environmental sensitivity using the HSC scale. The authors examined whether a collection of 87 SNPs in 16 candidate genes from the four subsystems of the dopamine (DA) including DA synthesis (Tyrosine hydroxylase [TH], Dopa Decarboxylase [DDC]), Dopamine beta-hydroxylase [DbH]), degradation/transport (*COMT, MAOA, MAOB, DAT1*), dopamine receptor (*DRD1, DRD2, DRD3, DRD4, DRD5*), dopamine modulation (Neurotensin genes [*NLN, NTS, NTSR1, NTSR2*]) would explain variations in HSC. They first conducted an ANOVA to examine which of the SNPS are significantly associated with sensitivity, and then conducted a regression with all the significant SNPs from the first step to explain their total and specific contribution to the trait. They found that ten SNPs were associated with sensitivity at the first step, and they together explained 10% of the variance in a sample of 480 Chinese students. The genes that significantly contributed to the explained variance were *DBH* and *DRD2* (DA receptor), and *NTSR1, NTSR2* and *NLN* (DA modulation). Interestingly, *DRD4*, *DAT1, COMT* and *MAOA* genes that have consistently been considered a marker of environmental sensitivity in GxE studies were not found to be significant contributors to trait sensitivity. The lack of associations for these candidate genes could partly reflect population stratification effects, since most previous studies consisted of Caucasians. Alternatively, this may be due to the two-step analytical procedure creating a competitive test of the dopaminergic system genes, rather than a straightforward association test with the trait. The results, however, underline the point raised earlier, that it cannot be assumed that the same genes from candidate GxE studies would be as relevant to the aetiology of the phenotype of general environmental sensitivity, and empirical evidence are thus required. The same limitation applies to the only genome-wide study by Keers et al. (2016), because the polygenic score of environmental sensitivity was constructed based on variation in response to environmental factors that bring about a specific outcome (emotional problems), rather than a general sensitivity to environmental influences. Apart from these two studies, there are no other candidate gene studies to have tested the assumed relationship between the phenotype of environmental sensitivity and candidate genes from GxE literature, or explored its genetic basis via genome-wide approaches; an important gap in research that will be the main aim of this chapter.

4.1.4 Aims

The main aim of this chapter was to identify the molecular genetic factors that contribute to individual differences in environmental sensitivity, as measured by the Highly Sensitive Personality scale (Aron & Aron, 1997). This was attempted through addressing the identified limitations and gaps in current research on molecular genetics of environmental sensitivity. As noted earlier, there are currently no hypothesis-free genome-wide studies of individual differences in environmental sensitivity, and although the candidate GxE studies reviewed so far provide an indication of what candidate genes may be involved, none bar one study by Chen et al. (2011) have tested their associations with the phenotype of environmental sensitivity. In addition, current research in the field has been limited to using candidate gene approaches, or testing associations at SNP levels only, and other more recent methods in the behavioural genetic field such as genome-wide polygenic risk scoring, gene-based, and gene-system analyses are yet to be employed.

These limitations and gaps in research were addressed in the current study by being the first to comprehensively examine the molecular genetics of environmental sensitivity, using both hypothesis-driven and hypothesis-free approaches. This was done by first using a candidate gene approach to test the associations between environmental sensitivity and variations in five VNTRs (*5-HTTLPR, DRD4, MAOA, DAT1, STin2*), as well as gene-based variations in 19 candidate environmental sensitivity genes identified from previous GxE studies. Second, an exploratory, hypothesis- free approach was taken by conducting a GWAS of environmental sensitivity, as well as using polygenic scoring, cross-trait genetic correlation, gene-level, and gene-pathway analyses to identify the genetic factors associated with individual differences in environmental sensitivity. The planned analyses were conducted in multiple samples. Three samples were used for the candidate gene approaches, including one from Belgium (N= 838), plus two from the UK (N= 395 and N= 642). Two datasets from the UK were used to conduct GWAS, gene-based, gene-system and polygenic score analyses. The polygenic score analysis was also used to take advantage of publically available GWAS summary statistics for thirteen phenotypes that have been associated with the environmental sensitivity phenotype (HSP) or candidate sensitivity genes. The phenotypes included the Big Five personality traits, depression and anxiety, as reported in **Chapter 2** and **3**, autism (Liss et al., 2008), ADHD (Brody et al., 2014), loneliness (van Roekel et al., 2011), and wellbeing/life satisfaction (Booth, Standage, & Fox, 2015). Insomnia and

educational attainment GWASs were also included due to their evidenced associations with a wide range of mental health outcomes and normal functioning (Bulik-Sullivan et al., 2015; Hammerschlag et al., 2017).

Being able to conduct the same analyses across independent samples ensures that any significant findings can be evaluated in light of their replicability. An important consideration for the planned analyses, especially because of the high possibility of false positive results in candidate gene approaches, due to lack of a robust knowledge of the biological relevance of the gene to mechanisms of environmental sensitivity, and also since the small samples for the genome-wide approaches makes them underpowered. In acknowledging the latter, a meta-analysis of GWAS results and other genome-wide analyses were also conducted, in order to enable better assessment of the results by increasing power and sensitivity. The large sample size from Belgium ensured the candidate gene studies were sufficiently powered to detect similar effect sizes as reported in previous candidate gene studies (see **Section 4.2.2.6** for power analysis).

4.2 Methods

4.2.1 Sample, measures and procedures

Three datasets were used to conduct the planned analyses in this chapter. Details of each dataset and the samples, measures, and the procedures used in the current study, are presented separately for each dataset in the following sections.

4.2.1.1 Twins Early Development Study (TEDS) Project

Sample: TEDS is a large longitudinal study of twins born in the UK between 1994 and 1996. Data were collected at ages 2, 3, 4, 7, 8, 9, 10, 12, 14, and 16. More information about TEDS is provided in **Chapter 2**, as detailed by Haworth, Davis, and Plomin (2012) . For the analyses in the current chapter, the data consisted of 647 individuals from TEDS for whom both genetic and phenotype data were available. The current sample did not include any twin pairs. Five individuals were later removed during QC procedures on the genotype data, as detailed in the next section. The final sample used in the analyses included 642 individuals (281 males, 361 females), with a mean age of 17.08 (*SD*= .87) at the time of phenotype data collection. The sample was ethnically homogenous with all individuals in the sample self-reported as White-British ethnicity.

Phenotype data: The 12-item Highly Sensitive Child (HSC) scale (Pluess et al., 2018) was used to measure environmental sensitivity. Detail on the development and psychometric properties of this scale are presented in **Chapter 2**. The data from the participants was collected via self-report online questionnaires, when participants were approximately 16 years old.

Genotype data: DNA was extracted from buccal swabs collected in two phases between 2007 and 2009 when TEDS participants were approximately 12 years old. Samples were collected from one member of each twin pair in participating families, to ensure that genetic data contained only unrelated individuals. DNA data was genotyped using Affymetrix Genome-wide Human SNP Array 6.0, SNPs imputed to 1000 genome reference panel using IMPUTE v2 and subjected to quality control following established pipelines, with the final imputed dataset of consisting of 5,237,380 SNPs. For the analyses in the current chapter, the available genotype data from TEDS were subjected to further quality control, using Coleman, Euesden, et al. (2016) protocol, as detailed in **Section 4.2.2.2.** The final dataset after all QC steps included 642 individuals and 3,220,761 common autosomal SNPs.

4.2.1.2 CogBIAS Project

Sample: CogBIAS is a 4-year longitudinal study of typically developing adolescents in Oxford, UK, conducted in three waves when participants were aged 12, 14 and 16 years old. The data collected through this study includes assessments on a range of cognitive processing tasks (e.g. attention bias, interpretation bias, memory bias) and psychological self-report measures (e.g. anxiety, depression, resilience, personality), as well as DNA data for those who had consented to contribute to genetic data collection (*N*= 916). More information on the project is detailed elsewhere (Booth et al., 2017) For the analyses in the current chapter, the data consisted of a subset of individuals from the larger dataset, for whom both genotype and phenotype data were available. HSC data was available for 424 participants, however there were no genetic data available for 12 of those, and 17 individuals were excluded following genotype data quality control as detailed in the next section. The final sample included 395 adolescents (177 males, 218 females), with mean age of 13.03 (*SD*= .77) at the time of data collection. The self-reported ethnicity was 83% White-European, 2% African/Caribbean, 1.8% East Asian, 4.8% South Asian, 0.3% Arab/Middle-Eastern, 3.8% mixed ethnicity and 4.3 % unknown.

Phenotype data: The Highly Sensitive Child (HSC) scale (Pluess et al., 2018) was used as the measure of individual differences in general sensitivity to environments, as in Study 1. Children who took part in the 2nd wave of CogBIAS data collection completed the questionnaire using pen and paper, in the classroom.

Genotype data: Saliva samples were collected at the first wave of data collection, using DNA Genotek Oragene OG-500 collection kits. The extracted genomic DNA was genotyped using the Illumina Human Omni express-24, which tags over 500k common SNPs from across the genome. Genotyped data were subjected to quality control using an established pipeline (Coleman, Euesden, et al., 2016), and additional SNPs were imputed (total SNPs = 5,596,260), using the 1000 Genomes phase 3 reference panel (The Genomes Project Consortium et al., 2015). For analyses in the current thesis, the available CogBIAS genotype data was subjected to further genotype quality control, using Coleman, Euesden, et al. (2016) protocol, as detailed in **Section 4.2.2.2**. The final dataset after all QC steps included 395 individuals and 5,595,637 common autosomal SNPs.

4.2.1.3 Studying Transactions in Adolescence: Testing Genes in Interaction with Environments (STRATEGIES) Project

Sample: STRATEGIES is a cross-sequential design study based on the development of internalising and externalising problems in a sample of adolescents (*N*= 1,111) recruited from nine schools in Flanders, Belgium. In the STRATEGIES project, adolescents from three age cohorts were assessed once per year during 5 consecutive years. The measures included parent, self and peer reports on a range of psychological measures such as externalising and internalising problems, social relationships and personality. DNA was extracted from saliva, collected at wave 1 (see next section for more information on genotype data). A total of 1,103 adolescents provided DNA data at the genotype data collection wave.

For the analyses in the current chapter, the sample consisted of all individuals for whom both phenotype and genotyped information were available. The sample size differed depending on the type of genetic data for analysis (VNTR or SNP data). Of the total sample of 979 individuals with phenotype data, 924 had data on at least one VNTR and 918 individuals had SNP data. The self-reported ancestry (grandparent's place of birth) of the sample was 843 White-Europeans, 67 non-Europeans and 14 unknowns. After removal of individuals with unknown or non-European ancestry (*N*=81), the number of

individuals with available VNTR data were *N*=838 for *STin2*, *N*=827 for *DAT1*, *N*=825 for *5-HTTLPR*, and *N*= 824 for *DRD4* and *MAOA*. The final sample size for those with SNP data, after removal of individuals with non-European ancestry and genotype data quality control steps was 838 (425 males, 413 females). The mean age of the sample was 14.76 (*SD*= .90).

Phenotype data: The Highly Sensitive Child (HSC) scale (Pluess et al., 2018) was used as a measure of individual differences in general sensitivity to environments, as in Study 1 and 2. HSC data were collected at the second wave of data collection, by visiting schools to assist participants in completing the questionnaire during a 50-minute session. In case the adolescents were not able to complete the questionnaire in time, they were asked to do so at home and return the completed questionnaire to the school within 2 weeks.

Genotype data: Genotype data in STRATEGIES included a selection of common SNPs as well as VNTRs. The DNA was obtained from saliva, collected via the Oragene DNA collection kits (DNA Genotek; Ontario, Canada).

VNTRs: Five candidate VNTRs were selected for genotyping according to research showing they are associated with sensitivity to the environmental influences. These included 40-bp DAT1, 48-bp *DRD4*, *STin2*, *MAOA* and *5-HTTLPR*. Polymerase chain reaction (PCR) followed by a fragment analysis protocol were used for genotyping. The amplification mixture for *5-HTTLPR, STin2 and MAOA* contained 12.5 µl Master Mix (Promega), 0.5 µmol/L of forward primers, 0.5 µmol/L of reverse primers, 50ng DNA and 1.5 µl water. The amplification mixture for PCR of *DAT1 and DRD4* included 50 ng genomic DNA, 12.5 µl Master Mix (Promega), 0.5 µmol/l of each forward and reverse primer, 1M Betaine solution (Sigma-Aldrich), and 1.5 µl water. The PCR cycling conditions lasted in total 64 minutes and 30 sec (see table for specific temperature in every phase). For the fragment analysis 0.5 µl of the PCR product with 0.5 µl GeneScan 600 LIZ Size Standard v2.0 (Applied Biosystems) and 10 µl Hi-Di formamide was used. After a denaturation (is a process in which proteins or nucleic acids lose the structure which is present in their native state) of 3 minutes at 95°C the analysis was conducted in an ABI 3730xl Genetic Analyzer (Applied Biosystems). The results were printed with GeneMarker software Version 1.91 (SoftGenetics, 2010). The fragment analysis was conducted for both alleles of the gene

separately. In the end, genetic information from these VNTRs was available for 97% of 1,116 students (1% not genotyped and 2% failed).

SNPs: Candidate SNPs in the original STRATEGIES data were selected using a step-wise procedure. First, an extensive literature search in PUBMED was conducted for candidate SNPs that had already been associated with various psychological constructs. Second, additional important SNPs per pathway were selected from the Search Tool for the Retrieval of Interacting Genes (STRING; Szklarczyk et al., 2011) dataset. Third, tagging SNPs were selected, that is, SNPs representative of the chromosomal region, based on a high linkage disequilibrium to predict a large amount of genetic variation by imputation, even though not every SNP in the region has been genotyped. Population data was obtained from the 1000 genomes project (The Genomes Project et al., 2012). Three Caucasian populations were used, the central Utah European descendants, Great Britain, and Tuscany Italy, as these were thought to resemble the targeted population. Candidate SNPs (i.e. from the first and second step) were included first and additional tagging SNPs (i.e. from the third step) were generated using Haploview (Barrett, Fry, Maller, & Daly, 2005). A total of 7,043 SNPs were selected and analysed using an Illumina Infinium iSelect Costum beadchip. Genotyped data were then subjected to quality control using established pipelines (Anderson et al., 2010; The International Schizophrenia Consortium, 2009), leaving a genotyped dataset of 5,052 common SNPs, in 344 genes known to be involved in nine neurotransmitter pathways (serotonin, dopamine, HPA-axis, oxytocin, GABA, Glutamate, Choline, Noradrenergic neurotransmission and the circadian clock pathway) and 1,031 adolescents (Van Assche et al., 2017).

For the current analyses, the genotype data in the sample with relevant phenotype data were subjected to further quality control, and additional SNPs were imputed to cover a larger proportion of the genome, using Michigan Imputation Server (Das et al., 2016), 1000 Genomes reference panel (The Genomes Project Consortium et al., 2015). The imputed data was quality controlled to remove poor quality and rare variants. The final dataset, after imputation and quality control steps, consisted of 65,671 SNPs and 838 Individuals. The QC steps and procedures are detailed in **Section 4.2.2.2.**

4.2.2 Analyses

This section provides an overview of the analytical approaches used in the current study as well as specific steps taken for each approach when analysing the data, including genotype quality control and power analysis.

4.2.2.1 Analytical approaches

In order to address the main aim of this chapter, i.e. to examine the molecular genetic basis of environmental sensitivity, two main analytical approaches were employed: a) candidate gene approach, whereby specific genetic factors were selected for analyses, because they were believed to be related to the phenotype of sensitivity based on theory and previous research; b) exploratory genome-wide approach, whereby there were no a-priori hypotheses for the examined genetic factors, instead available genome-wide data were tested for their association with sensitivity. Within these approaches, genetic associations between single Nucleotide Polymorphisms (SNPs), genes, and biological systems, using Genome-Wide Association Study **(**GWAS), gene-based and gene-set analyses, respectively, were examined. In addition to examining the association between single genetic variants and sensitivity, as in GWAS, polygenic score analyses were also conducted to examine the combined additive contribution of multiple SNPs to sensitivity. Lastly, in order to test replicability of findings and increase the power in the study, all of the analyses were first conducted separately in available datasets, followed by meta-analysis of GWAS results, gene-based and gene-set analyses. As well as increasing the sample size and power, the meta-analysed results account for different characteristics of each sample (age group, ethnicity mix, genotyping chips).

Different data sets were used for the planned analyses, depending on the specific genetic information that they contained. The imputed TEDS and CogBIAS datasets contained genome-wide data of over 3 million common SNPs, and STRATEGIES contained over 60,000 SNPs and 5 VNTRs (*5-HTTLPR, DAT1, STin2, MAOA*, and *DRD4*). **Table 4.2** at the end of this section shows a summary of the samples used in each analytical step. The approaches used in the current chapter are briefly described below:

Candidate gene analysis typically tests the association between a phenotype and base-pair change in a single SNP, or number of repeats in a VNTR. Depending on the literature and biological hypothesis, the alleles may be coded as additive, recessive or

dominant genetic models. For the candidate gene approach in the current chapter, the VNTRs were coded in a dominant as well as additive genetic model informed by literature.

GWAS is the gold-standard method of examining genetic differences at the SNP level, by comparing the prevalence, or strength of an association between a phenotype and changes in base-pair units, to infer which variants are most relevant to the phenotype of interest, using t-tests for quantitative traits (or regression if there are covariates). Multiple testing correction is usually applied to results to account for type I error, with $p< 5x10^{-8}$ as the commonly used threshold. For the current chapter, GWAS were conducted on TEDS and CogBIAS datasets, using linear regression model, with age, gender and principal components as covariates. Linear regression, rather than a mixed model was used, as it has been shown that in data sets that do not contain family structure or cryptic relatedness, simpler association tests with principal component correction are sufficient (Price et al., 2006; Price, Zaitlen, Reich, & Patterson, 2010).

Meta-analysis combines the evidence for association from individual studies to provide a more accurate estimate of effect. Meta-analysis can also increase the power in downstream genetic analyses, by increasing the total sample size. Meta-analysis results in little or no loss of efficiency compared to analysis of a combined dataset that includes data from individual in different studies. Running separate analyses on each data set and then meta-analyzing the results, rather than analyzing the combined data, has the added advantage of being able to control for sample specific covariates, rather than assuming they are similar enough to reflect the same population. The two common approaches in meta-analysis are to either use test statistics and standard errors (SE model) or the p-values across studies (Z-score). While both methods are comparable, the first approach weights the β-coefficients by their estimated standard errors, and is suitable if the effect size estimates and their standard errors are in consistent units across studies, while the second approach takes into account the differences in sample size and direction of effect into account. For the current study, the standard-error based model were deemed more suitable because the same measurement units were used across studies and the follow up polygenic score analyses make use of the effect size (beta-coefficient values) when constructing the scores.

Gene-based analysis summarises the effects of all SNPs in each gene into a single statistic, and then examines this statistic in order to identify the gene most significantly associated with variations in a trait. The gene statistics are commonly obtained via three main methods: a) aggregating the effects of SNPs in a gene (SNPwise-mean model); b) selecting one/several of the top most strongly associated SNP(s) in the gene (SNPwise-top model); c) regressing the phenotype on principal components derived from the SNPs in a gene (principal component regression model), which is sensitive to mean level of association and has better power to detect associations in low LD areas. There are limitations in all three approaches, where the model skews towards associations in areas of higher LD in a gene (model a), or the model is sensitive only when a small proportion of SNPs in a gene show association (method b), or is less sensitive when only a small proportion of SNPs is associated (model c). A more recent method by de Leeuw, Mooij, Heskes, and Posthuma (2015) aggregates the p-values obtained from all three gene-based models to counter the biases in each model and increase sensitivity to a wider range of genetic architectures (multi-model). The gene-based analysis is suited to genome-wide data, though it can also be conducted on a selected number of genes. The multi-model option of MAGMA (de Leeuw et al., 2015) was used for the gene-based analyses in this chapter, which best account for differences in the genetic architecture.

Gene-set analysis involves the examination of the association between the phenotype and genetic variation in curated sets of genes deemed to be implicated in specific biological pathways/networks/functions. The associations are commonly examined in two ways: a) competitive gene-set test and self-contained gene-set test. In the competitive gene-set test, the mean association with the phenotype in a target gene-set is compared to the mean association outside of the target gene-set. The null hypothesis here is that there are no differences between the target gene-set and random gene-sets of similar properties (gene size, density, minor allele count and per gene sample size). While this test indicates how a gene-set compares to others, it does not determine how strongly it is associated with the trait. In contrast, the self-contained test examines the mean association within a gene-set, as opposed to comparing it to other gene-sets. The null hypothesis is that none of the genes in the gene-set are associated with the trait. The test effectively is an omnibus gene test, as to whether at least one gene in the gene set is associated with the phenotype. Though this test does indicate how strongly the gene-set is associated with the trait, it does not determine how important it is compared to other

gene-sets. Both approaches were used to conduct gene-set analysis in the current chapter.

Polygenic score analysis examines the collective contribution of hundreds to thousands of SNPs to variation in the phenotype of interest. To do this, the results of an initial GWAS (discovery sample) are used to construct a polygenic score in a second sample (target sample). This score is the sum of associated alleles weighted by their effect size (e.g. β- coefficient). Several scores are calculated, including SNPs with p-values that surpass a specified threshold. Linear or logistic regression is then conducted to test how much of the variation in the phenotype is predicted by the polygenic scores at each threshold. Polygenic score analysis therefore examines the collective contribution of multiple SNPs to a trait, rather than identifying single SNPs with statistically significant effects on the trait, a genetic model that is more compatible with the current understanding of the genetics of complex traits (Visscher et al., 2017). For the current chapter, 3 sets of polygenic score analyses were conducted, in order to a) predict environmental sensitivity in CogBIAS from TEDS summary statistics; b) predict sensitivity in CogBIAS from summary statistics of the GWAS of differential susceptibility in Keers et al. (2016) study; c) predict sensitivity in TEDS and CogBIAS based on summary statistics of thirteen publically available GWASs on personality (neuroticism, extraversion, openness, conscientiousness, agreeableness) and a range of disorders and outcomes (autism, ADHD, anxiety, depression, insomnia, loneliness, wellbeing). For analysis "a", TEDS was used as the discovery sample, since using a larger dataset for the discovery sample is a recommended approach, affording more power to the study (Dudbridge, 2013). For analysis "b", only CogBIAS sample was used, due to the sample overlap between Keers et al. (2016) study and TEDS participants in the current study. For analysis "c", these GWASs were selected based on their hypothesised and evidenced phenotypic and genetic associations with environmental sensitivity, as detailed in **Chapter 2** and **Chapter 3.**

In addition to cross-trait analyses in separate TEDS and CogBIAS data, another option in PRSice, Sum-Sum scores, was used which utilizes GWAS summary data in both the base and target data sets to evaluate evidence for shared genetic aetiology, using the method of Johnson (2013). This approach was used to conduct genetic correlation analyses on the meta-analysed TEDS-CogBIAS GWAS data and the summary statistics from the available GWASs of personality and psychopathology. Using the meta-analysed datasets provides more power since the target dataset is larger, as well as

allowing to test whether the findings from the polygenic score analysis that have been conducted separately in TEDS and CogBIAS hold true. **Table 4.2** shows a summary of the data sets and the relevant analyses conducted in each data set.

Table 4.2 Summary of data sets used in the current chapter and the relevant analyses

Dataset	Sample Characteristics		Candidate gene analyses		Genome-wide analyses *				
	Sample N	N SNPs	Candidate VNTR	Candidate gene	GWAS	Meta-analysis	PGS of sensitivity	PGS of DS	Cross-trait PGS
TEDS	642	3,220,761	×	✓	✓	✓	✓Discovery	×	✓Target
CogBIAS	395	5,595,637	×	✓	✓	✓	✓Target	✓Target	✓Target
STRATEGIES	838	65,639 & 5 VNTRs	✓	✓	×	×	×	×	×
GWAS of differential susceptibility [a] (Keers et al., 2016)	1026	679,050	×	×	×	×	×	✓Discovery	×
GWAS of depression [b] (Okbay, A. et al., 2016)	180,866	6,524,474	×	×	×	×	×	×	✓Discovery
GWAS of educational attainment [b] (Okbay, Aysu et al., 2016)	293,723	8,146,840	×	×	×	×	×	×	✓Discovery
GWAS of neuroticism [b] (Okbay, A. et al., 2016)	170,911	6,524,432	×	×	×	×	×	×	✓Discovery

Table 4.2 Continued

Dataset	Sample Characteristics		Candidate gene analyses		Genome-wide analyses *				
	Sample N	N SNPs	Candidate VNTR	Candidate gene	GWAS	Meta-analysis	PGS of sensitivity	PGS of DS	Cross-trait PGS
GWAS of extraversion [c] (van den Berg et al., 2016)	Sample N	N SNPs	Candidate VNTR	Candidate gene	GWAS	Meta-analysis	PGS of sensitivity	PGS of DS	Cross-trait PGS
GWAS of openness [c] (de Moor et al., 2012)	17,375	2,305,640	×	×	×	×	×	×	✓Discovery
GWAS of agreeableness [c] (de Moor et al., 2012)	17,375	2,305,461	×	×	×	×	×	×	✓Discovery
GWAS of conscientiousness [c] (de Moor et al., 2012)	17,375	2,305,682	×	×	×	×	×	×	✓Discovery
GWAS of ADHD [d] (Demontis et al., 2017)	55,374 (20,183 cases 35,191controls)	8,094,094	×	×	×	×	×	×	✓Discovery
GWAS of autism [d] (Autism Spectrum Disorder Working Group of the Psychiatry Genomics Consortium, 2015)	13,574 (6,197 cases 7,377 controls)	6,440,259	×	×	×	×	×	×	✓Discovery

Table 4.2 Continued

Dataset	Sample Characteristics		Candidate gene analyses		Genome-wide analyses *				
	Sample N	N SNPs	Candidate VNTR	Candidate gene	GWAS	Meta-analysis	PGS of sensitivity	PGS of DS	Cross-trait PGS
GWAS of anxiety [d] (Otowa et al., 2016)	18,000	6,306,612	×	×	×	×	×	×	✓Discovery
GWAS of loneliness [d] (Gao et al., 2016)	7,556	5,768,558	×	×	×	×	×	×	✓Discovery
GWAS of insomnia [e] (Hammerschlag et al., 2017)	113,006 (32,384 cases 80,622 controls)	12,444,915	×	×	×	×	×	×	✓Discovery
GWAS of subjective wellbeing [a] ** (Okbay, A. et al., 2016)	202,818	2,268,371	×	×	×	×	×	×	✓Discovery

*Cross-trait PGS analyses were also conducted on the meta-analysed TEDS-CogBIAS GWAS and all 13 consortium data; a= Data obtained from Authors; b= Data obtained from SSGAC (https://www.thessgac.org/data); c= Data obtained from Genetics of Personality Consortium (http://www.tweelingenregister.org/GPC/); d= Data downloaded from Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/results-and-downloads); e= Data downloaded from (https://ctg.cncr.nl/software/summary_statistics); PGS= polygenic score; DS= differential susceptibility

** This data set includes GWAS summary statistics with TEDS participants excluded, provided by the first author.

4.2.2.2 Genotype data quality control and population stratification

Genotype data quality control were conducted in each data set, by examining SNP frequency, per-individual and per-SNP missingness, Hardy-Weinberg equilibrium, population stratification and ancestry, and unusual patterns of heterozygosity. SNPs with minor allele frequency (MAF) < .01, individual and SNP missingness rates of over 1%, deviation from HWE (p-value < $1x10^{-6)}$, cryptic relatedness (IBD> .1875) and heterogeneity > 3 *SD* were removed from the data. **Figures 4.1a, 4.1b** and **4.1c** show the quality control process for each data set.

Figure 4.1a Quality Control Process – TEDS data

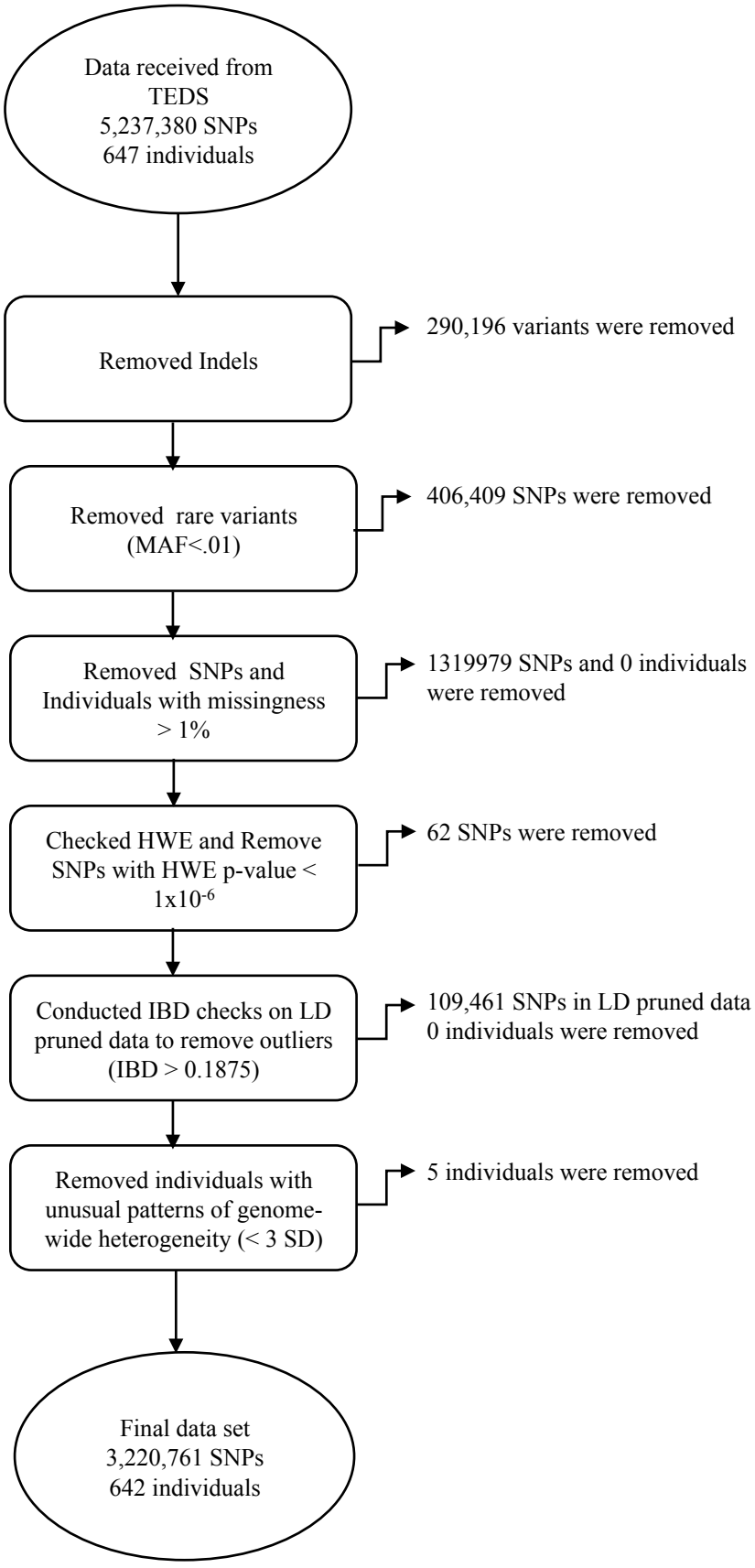


Figure 4.1b Quality Control Process – CogBIAS data

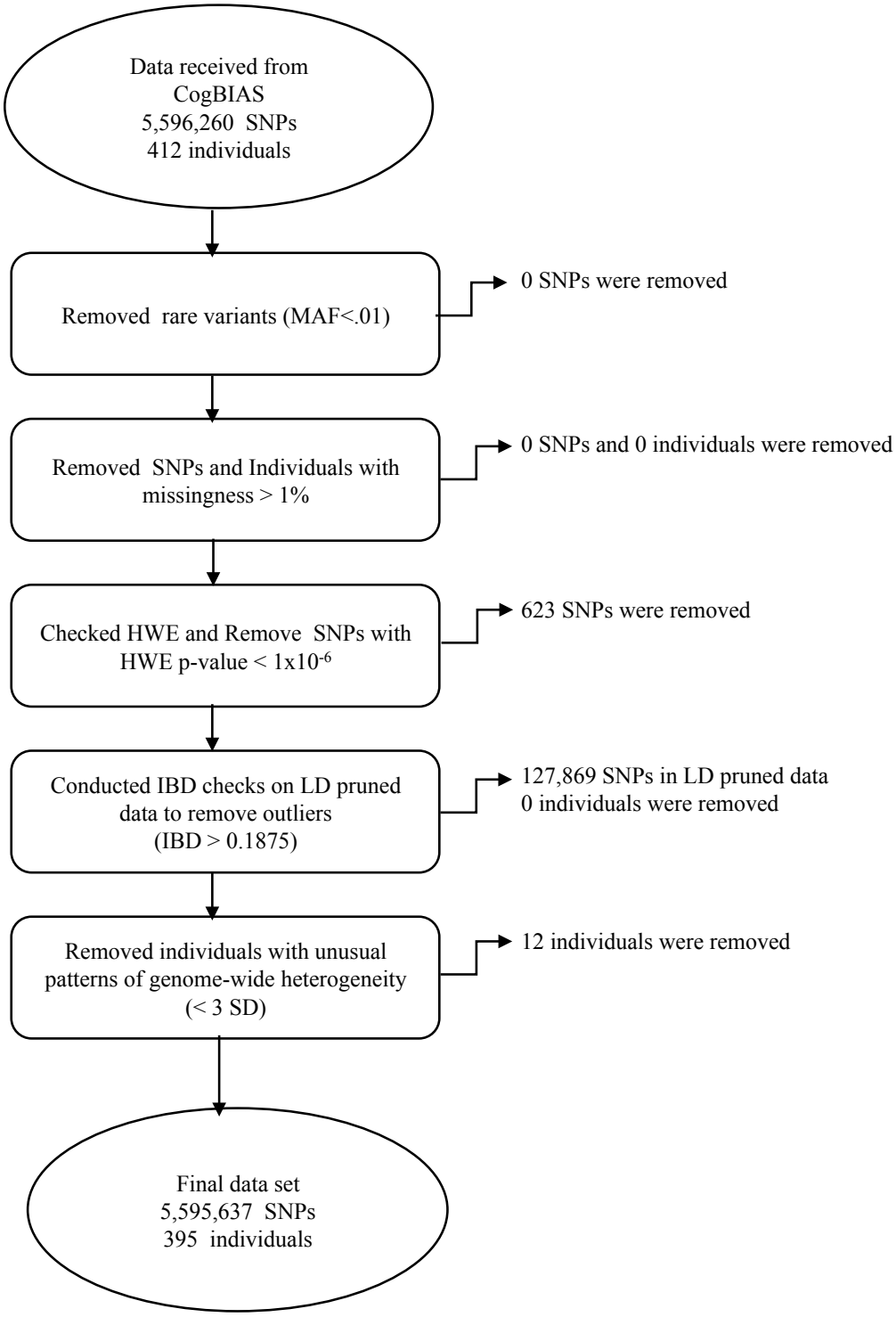
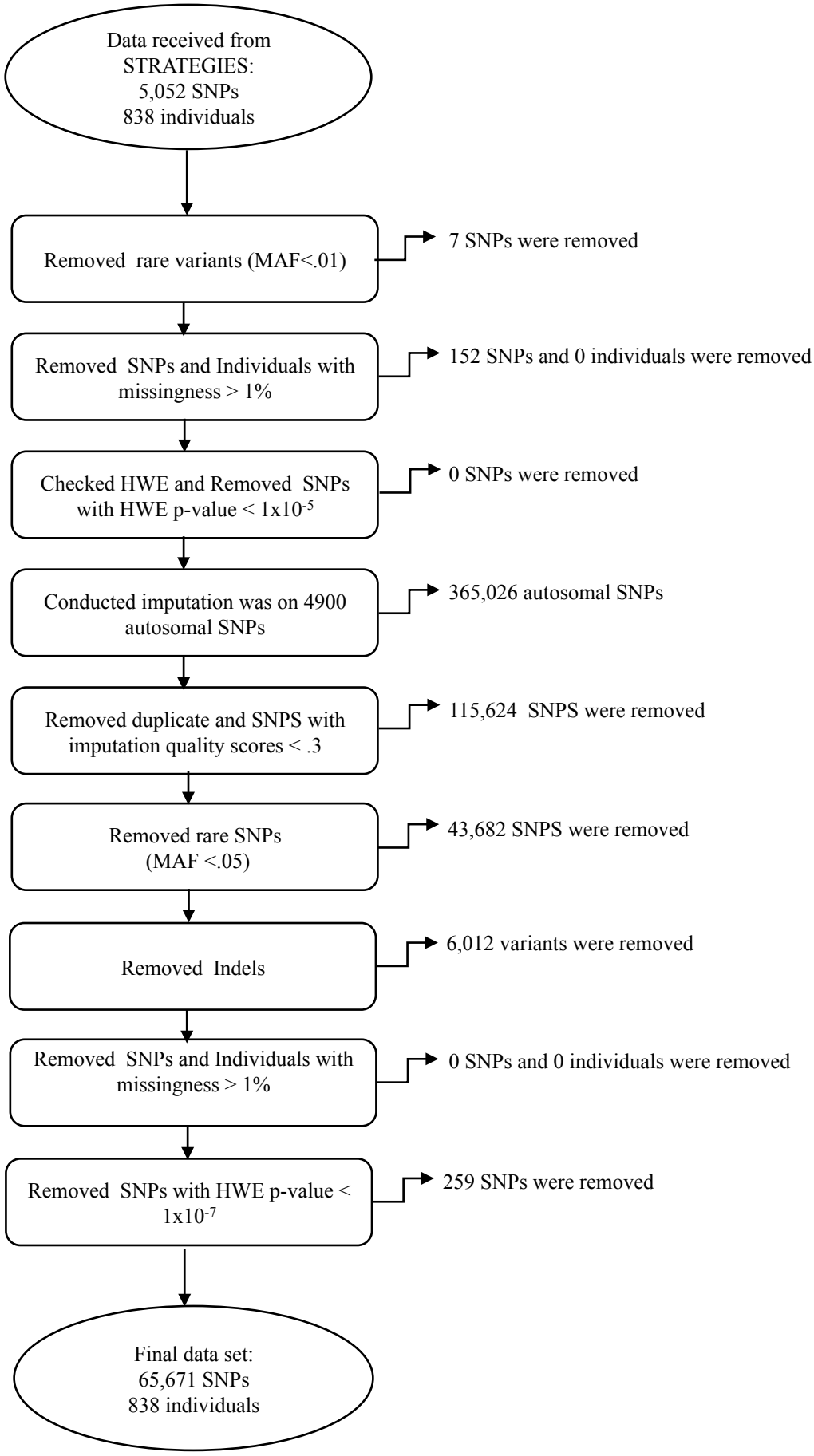


Figure 4.1c Quality Control Process – STRATEGIES data



Population structure of TEDS and CogBIAS were examined via Principal Component analysis, using the smart-pca program of the EIGENSOFT version 6.1.4, which uses population genetic methods of Patterson, Price, and Reich (2006) to account for population structure. First, smart-pca was run to generate 100 principal components (PCs) from the LD-pruned genotype data and a scree-plot of the pcs was created. Second, A Tracey-Widom test was conducted to evaluate the statistical significance of each principal component identified by PCA. Third, Smart-pca was conducted again to check for, and remove, any individual outliers (3 *SD*) on the significant principal components. Finally, a series of linear regressions were conducted to examine the phenotypic variance explained by each component, and when added to a model including the previous components. Decision on how many pcs to include as covariates in the genetic analyses was based on the scree plot of the pcs from PCA, Tracey-Widom test, and association between PCs and phenotype. **Figures 4.2a** and **4.2b** show the process in TEDS and CogBIAS.

Figure 4.2a PCA Process – TEDS data

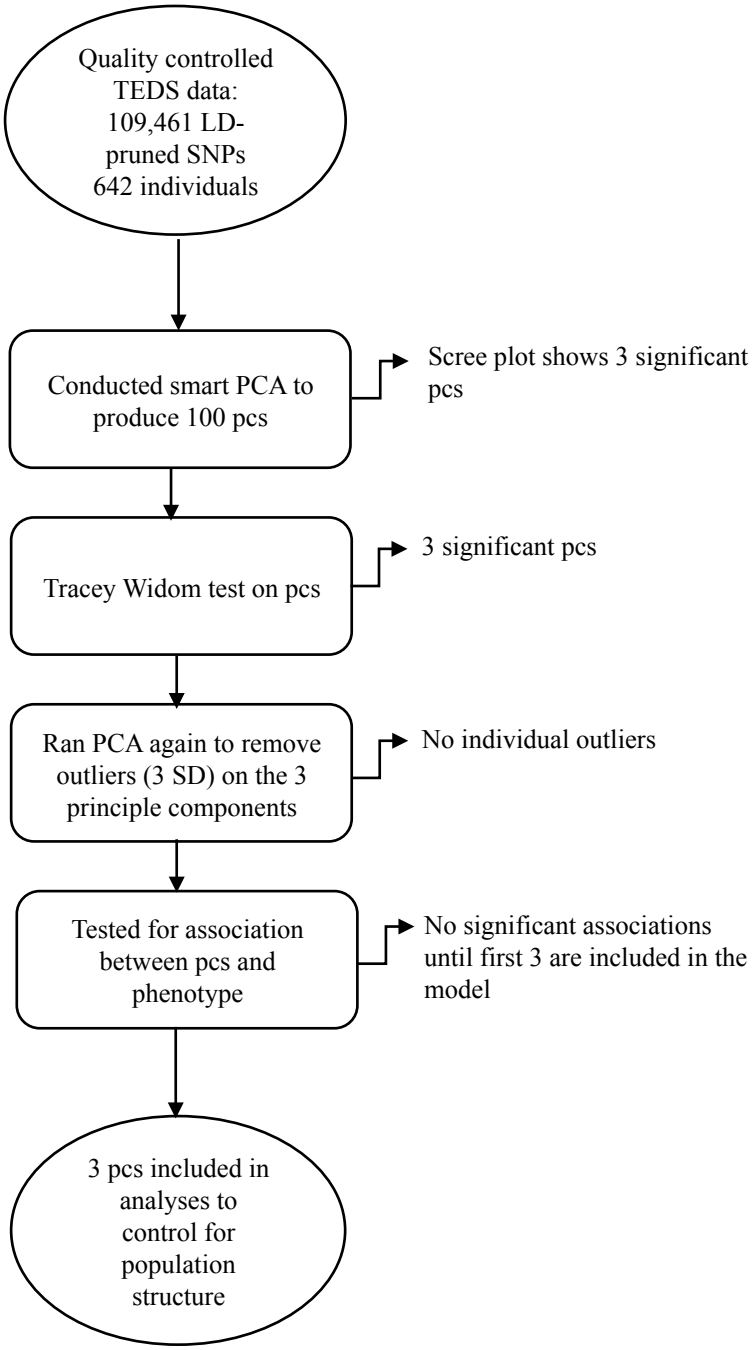
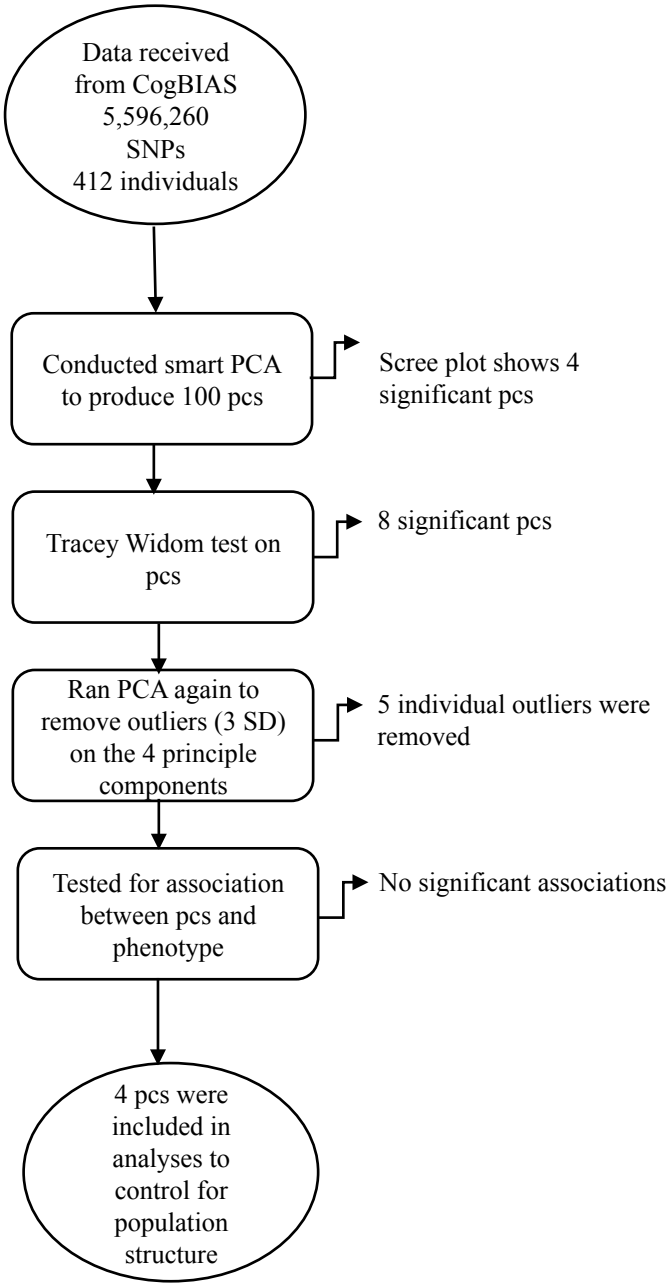


Figure 4.2b PCA Process – CogBIAS data



In TEDS, the scree plot of eigenvalues showed no significant pcs (**Figure 4.3**). The Tracey-Widom test indicated 3 significant PCs (**Table 4.3**), but there were no individual outliers on the 3 PCs. The results of regressing the PCs on the phenotype showed there were no significant associations with sensitivity until the first 3 PCs were added to the model (R^2= .01, p< .05). Though all Eigenvalues were below 1.2, and Tracey-Widom test did not identify significant PCs, a more conservative approach was taken to include 3 PCs as covariates in the analyses to correct for population stratification effects in TEDS, because the first 3 components together were significantly associated with sensitivity.

In CogBIAS, the scree plot of eigenvalues showed 4 significant PCs (**Figure 4.3**). The Tracey-Widom test identified 8 significant PCs (**Table 4.3**). There were 5 individual outliers on the 4 PCs, which were removed from the data. After removal of outliers, the Tracy-Widom test indicated 6 significant PCs (**Table 4. 3**). The results of regressing the PCs on the phenotype showed there were no significant associations between the PCs and sensitivity. Though the PCs were not significantly associated with sensitivity, the scree plot showed an elbow (considerable drop eigenvalue) after 4 pcs, therefore it was decided to include the first 4 principal components as covariates in the analyses to correct for population stratification effects in CogBIAS.

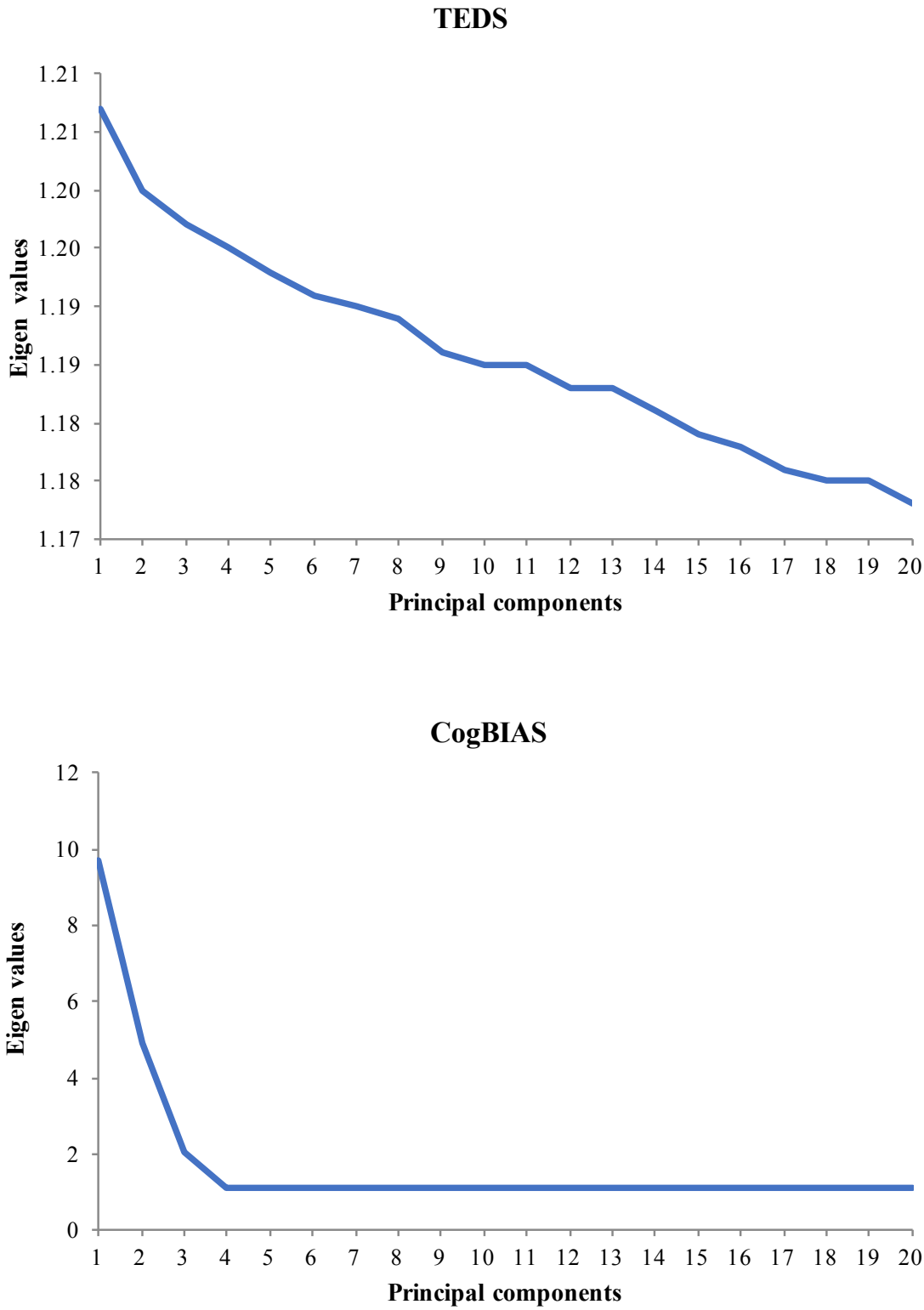


Figure 4.3 Scree plot of principal components in TEDS and CogBIAS

Table 4.3 Tracy-Widom test of significant principal components in TEDS and CogBIAS

	TEDS			CogBIAS (prior to removal of individual outliers)			CogBIAS (after removal of individual outliers)		
PCs	Eigen	TW stat	*P*	Eigen	TW stat	*P*	Eigen	TW stat	*P*
1	1.20	2.24	**6.9E-03**	10.24	507.82	**0.0E+00**	9.72	504.88	**0.0E+00**
2	1.20	2.03	**9.9E-03**	4.97	683.57	**0.0E+00**	4.93	674.69	**0.0E+00**
3	1.19	1.72	**1.6E-02**	2.05	480.13	**0.0E+00**	2.05	479.60	**0.0E+00**
4	1.19	-0.57	2.9E-01	1.19	47.52	**7.6E-97**	1.13	11.79	**1.5E-13**
5	1.19	-1.49	5.7E-01	1.14	16.18	**1.0E-20**	1.12	4.09	**1.8E-04**
6	1.19	-2.30	8.0E-01	1.12	3.00	**1.7E-03**	1.12	1.44	**2.6E-02**
7	1.18	-2.67	8.8E-01	1.12	1.54	**2.2E-02**	1.11	0.06	1.6E-01
8	1.18	-4.64	1.0E+00	1.11	1.01	**4.8E-02**	1.11	0.26	1.3E-01
9	1.18	-4.48	1.0E+00	1.11	0.27	1.2E-01	1.11	-2.42	8.3E-01
10	1.18	-5.42	1.0E+00	1.11	-0.88	3.8E-01	1.11	-2.54	8.6E-01

Associations with $p < .05$ are in bold

The genetic ancestry of the samples were also examined, by using 1000 Genomes Phase 1 data (The Genomes Project Consortium et al., 2015) and plotting individuals on PCs drawn from the reference populations. **Figures 4.4a** and **4.4b** show the samples from each dataset projected onto 1000 Genomes population data, with the TEDS and CogBIAS sample clustering on the European-British population as would be expected from the self-report ethnicity data.

Figure 4.4a Ancestry checks - TEDS data

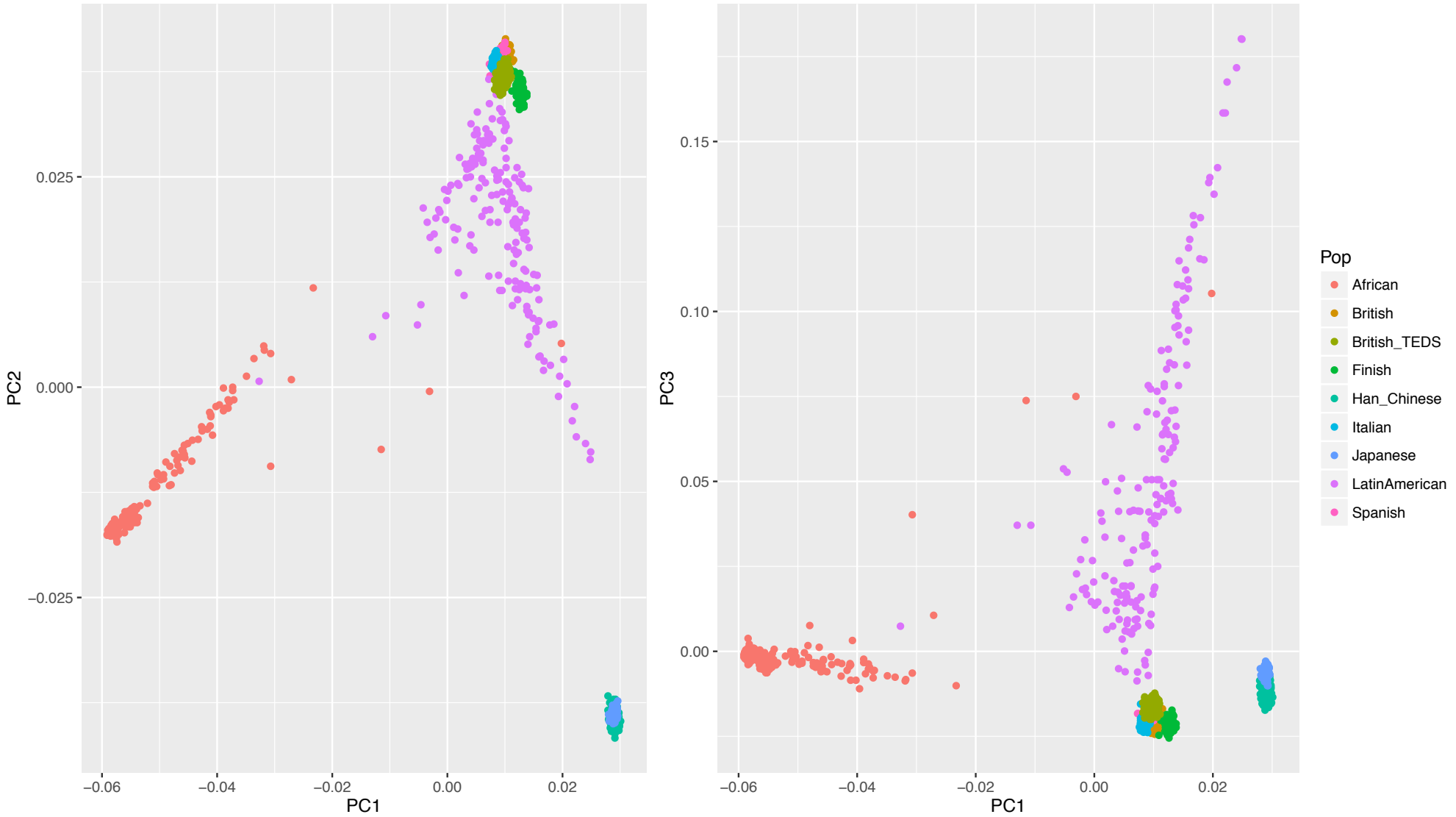
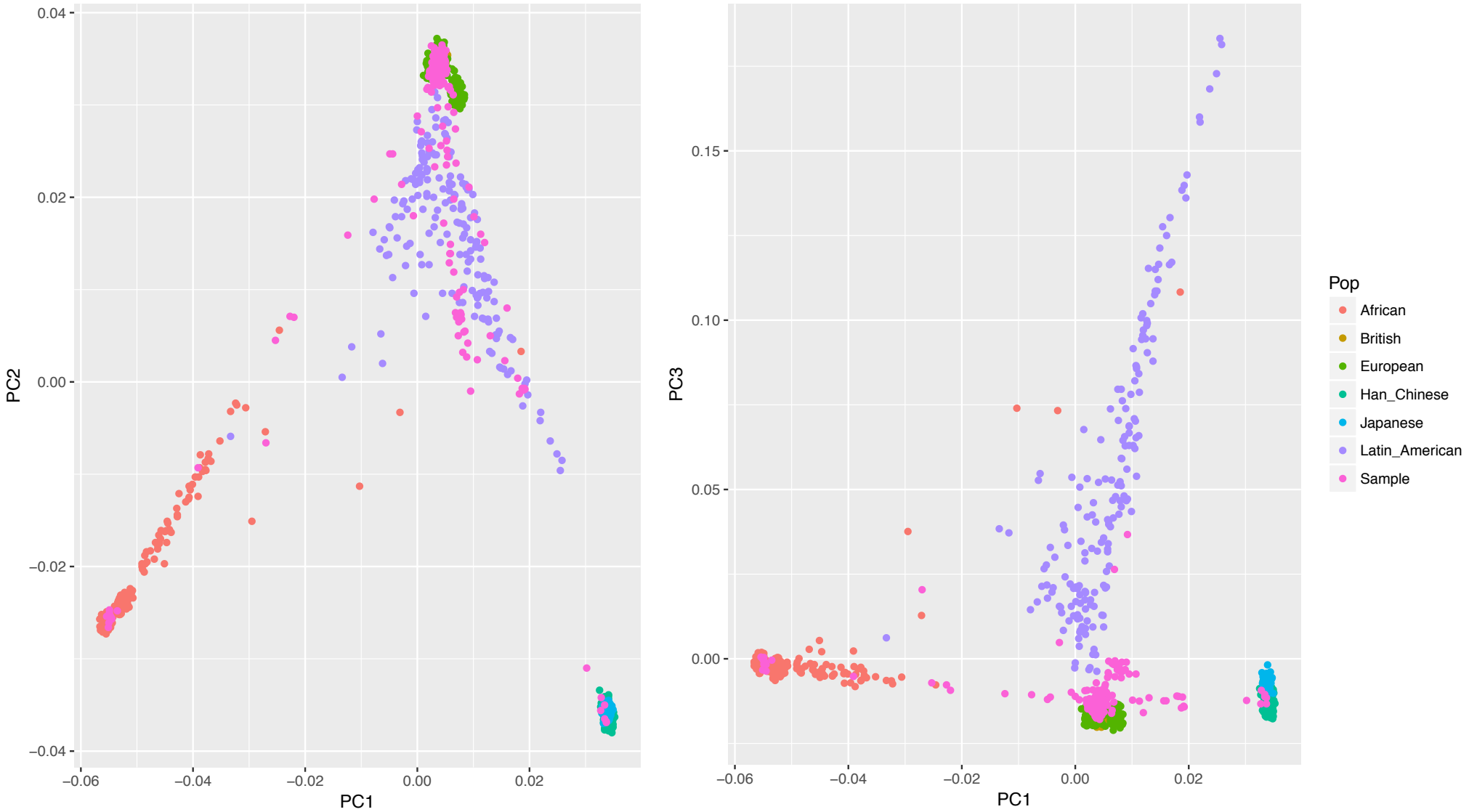


Figure 4.4b Ancestry checks - CogBIAS data



4.2.2.3 Analysis steps: candidate gene approaches

The aim of this set of analyses was to examine whether any of the candidate genes that have been previously reported to reflect sensitivity to environmental influences would be associated with the phenotype environmental sensitivity, measured with the HSC scale. This was achieved through the following steps:

First, the association between five VNTRs and sensitivity were examined in STRATEGIES data. This was done by first obtaining allele frequencies for each VNTR in the data, and examining their deviation from Hardy-Weinberg Equilibrium, using Hardy Weinberg package in R. Then, genotypes were coded in either an additive (*5-HTTLPR, DAT1, STin2*) or dominant (*DRD4, MAOA*) genetic model, according to previous studies within a differential susceptibility framework (Belsky et al., 2014). Linear regression analyses were then conducted separately for each VNTR, with sensitivity as the outcome and the VNTR as the predictor, with age and sex as covariates. The analyses on *MAOA* were conducted for males and females separately, due to males only having one X-chromosome where *MAOA* is located.

Second, the association between differential susceptibility candidate genes and sensitivity were examined across the three datasets. This was done by first annotating the 19 candidate environmental sensitivity genes identified through previous literature (see **Table 4.1a** and **1b**, **Section 4.1.2.2**) to the SNPs in each data set, using the NCBI (build 37) genomic loci (annotation window =20kb). Of the 19 genes, two were not available in STRATEGIES data. The multi-model option of MAGMA was then used to examine the associations in TEDS and CogBIAS, with PCs, age and gender as covariates, and in STRATEGIES, with age and gender as covariates.

4.2.2.4 Analysis steps: genome-wide approaches

The aim of this set of analyses was to employ a range of hypothesis-free approaches to examine the genetic basis of environmental sensitivity. First, GWAS were conducted on quality-controlled TEDS and CogBIAS data, using a linear regression model, with age, gender and principal components as covariates.

Second, individual GWAS results from TEDS and CogBIAS were meta-analysed. This was done by first harmonising data using Genotype Harmonizer (Deelen et al., 2014) to ensure both COGBIAS and TEDS datasets were aligned to the same genomic strand, followed by filtering of the genetic data so that each dataset contained only SNPs that

are common to both (NSNPs= 2,545,244). Next, a GWAS was conducted separately on each data set, using a linear regression model with their respective PCs, age, and gender as covariates. The two GWAS results were meta-analyzed using METAL (Willer, Li, & Abecasis, 2010), via the Standard Error method. Two additional METAL options were also selected to: a) implement Cochran's Q-test for heterogeneity of effects across samples and b) estimate and apply genomic control correction to input statistics prior to performing meta-analysis.

Third, gene-based analyses were conducted on TEDS and CogBIAS separately. This was done by first annotating the SNPs in TEDS and CogBIAS to 19,427 functional (protein-coding) genes from the NCBI built 37 (annotation window =20 kb), and then using the multi-model option in MAGMA for analyses with age, gender and PCs as covariates. The results of the gene-based analysis from TEDS and CogBIAS were then meta-analysed using the meta-analysis option in MAGMA, which uses the weighted Stouffer's Z method is used to combine the Z-scores for each gene across cohorts, with weights set to the square root of the sample size each Z-score is based on.

Fourth, the gene-set analyses were conducted on TEDS and CogBIAS separately. To do this, genes were annotated to 10,648 gene sets from Broad Institute MsigDB v5.2 (Subramanian et al., 2005). This included of 5,917 gene-sets from three GO terms (biological process: 4,436 gene sets; cellular component: 580 gene sets; molecular function: 901 gene sets), and 4,731 curated gene-sets from five other data sources (chemical and genetic perturbations: 3,402 gene sets; Canonical pathways: 1,329 gene sets; BioCarta: 2,17 gene sets; KEGG: 186 gene sets; Reactome: 674 gene sets). Competitive and self-contained tests were then conducted on TEDS, CogBIAS and the meta-analysed gene-based results.

Fifth, polygenic score analyses were conducted on TEDs and CogBIAS, and the meta-analysed GWAS data using PRSice. The polygenic score analyses were conducted three times: first, to examine the polygenic scores of environmental sensitivity in the CogBIAS sample from the summary statistics of GWAS of environmental sensitivity in TEDS; second, to examine the polygenic scores of environmental sensitivity in the CogBIAS sample from the summary statistics of a GWAS of differential susceptibility from Keers et al. (2016); third, to predict environmental sensitivity in TEDS and CogBIAS from polygenic scores derived from summary statistics of publically available GWASs on personality traits (neuroticism, extraversion, openness, conscientiousness,

agreeableness) and other outcomes (autism, ADHD, anxiety, depression, insomnia, loneliness, wellbeing, educational attainment). PRSice was used to construct polygenic scores at nine *P*-value thresholds (P_T= .001, .01, .05, .10, .20, .30, .40, .50, 1) on pruned data, using default clumping options (*p*-value threshold= 1, LD cut off r^2= .1, threshold window = 250kb), after excluding the major compatibility complex region of the genome since the long-range linkage disequilibrium in this region makes linkage equilibrium difficult to obtain. High resolution polygenic scoring was also conducted, whereby for each individual, there were PGS for all *P*-value thresholds between .0001 and .50 at .0005 increments. Age, sex and PCs were included as covariates in the regression model predicting sensitivity. For the meta-analysed GWAS data, the 1000 genomes European panel (The Genomes Project Consortium et al., 2015) was used to clump the data, with more stringent clumping parameters (*p*-value threshold= .5, LD cut off r^2= .05, threshold window=300kb), as per the PRSice recommendation (Euesden, Lewis, & O'Reilly, 2015).

4.2.2.5 Statistical programs and software

R was used to examine the associations between candidate VNTRs and sensitivity as well as other descriptive statistics. PLINK1.9 (Chang et al., 2015) was used to conduct QC steps and GWAS analyses. FUMA (Watanabe, Taskesen, van Bochoven, & Posthuma, 2017) was used for annotation of GWAS results and graphics. METAL (Willer et al., 2010) was used to conduct the meta-analyses of the GWAS results. MAGMA (de Leeuw et al., 2015) was used to conduct gene-based and gene-set analyses. PRSice (Euesden et al., 2015) was used for the polygenic score analyses.

4.2.2.6 Power analysis

Power of a study is determined by several factors, including the sample size, the type of statistical analysis, the significance threshold, and the expected effect size of the variables on the outcome. In terms of power, more stringent significance thresholds, larger number of variants and smaller effect sizes require larger samples to account for probability of type I and type II errors. In order to calculate the power of the current study for the planned analyses and the available sample sizes, an estimation of the expected effect sizes is required.

With regards to genetic effect sizes, genetic association studies commonly report that a biologically plausible effect size for a single polymorphism or single interaction on

common traits is very small (explained variance < .02%) (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015; Rietveld et al., 2013). The very small effect sizes are typical of GWAS analyses, since each SNP is assessed for its association with the phenotype. Therefore, in order for these small effects to be identified, very large sample sizes are required. Indeed, evidence from recent studies indicate that improving the power through larger samples is an important factor in identifying larger number of replicable genetic variants of small effects, as has been seen in GWAS of Schizophrenia for example (Ripke et al., 2014; Ripke et al., 2013; Ripke et al., 2011).

Polygenic approaches are expected to explain more of the variance in complex traits, since such studies summarise the cumulative effect of hundreds to thousands of genetic variants in a single score for use as the predictor variable. Despite this, the expected explained variance tends to be small, with most recent studies with over 100,000 participants showing polygenic scores explain less than 10% of the variance (typically 2-3%) in common traits (Rietveld et al., 2014; Rietveld et al., 2013).

Although there are currently no genome-wide studies of the environmental sensitivity phenotype, effect sizes are expected to be small, in line with findings reported for other GWAS of complex traits. The only previous study of trait environmental sensitivity by Chen et al. (2011) showed surprisingly large genetic effects. Single SNPs explaining almost 4% of the variance in in highly sensitive personality scores (F= 4.98, Cohen's d= .39, η^2= .04). Nevertheless, these large effect sizes are at odds with those reported in other studies of complex traits with exponentially larger sample sizes and therefore likely reflect type 1 errors. Chen et al. (2011) also reported that polygenic score comprising just 10 SNPs explained as much as 11% of the variance in highly sensitive personality. However, it is likely that the unusual two-stage analysis used to create this score led to an inflation of genetic effects. Specifically, Chen et al. (2011) first tested a large number of SNPs for their association with the phenotype using an ANOVA. In a second step, they then selected the most significantly associated SNPs and included them in a linear regression to examine the extent to which they collectively predicted sensitivity in the same sample. While such an approach is possible with two separate samples, using the same participants in both discovery and target samples in this way results in substantial over-fitting of the linear regression model and subsequent inflation of genetic effects.

For the current study, power analyses were conducted using G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009), in order to determine the power to detect the expected genetic effect sizes, in linear multiple regression (fixed model, R^2 deviation from 0) in each sample, with 3 predictors in STRATEGIES (VNTR/gene + age + gender) and 6 in TEDS (SNP/ gene/gene-set/PGS + age + gender + 3PCS) and 7 in CogBIAS (SNP/ gene/gene-set/PGS +age+ gender + 4PCS).

The power analyses were conducted for effect sizes between .01% to 10% in each sample, at uncorrected alpha threshold (α= .05) as well as the multiple -testing -corrected thresholds. For GWAS, $5x10^{-8}$ threshold was used to correct for multiple testing as is customary in the field. For candidate gene analyses, gene-based, and gene-set analyses, power was calculated for Bonferroni corrected alpha thresholds (α= .01 for VNTR analysis; α= .003 for candidate gene-based analyses; α=2E-06 for genome-wide gene-based analyses; α= 5e-06 for genome-wide gene-set analyses). For polygenic score analyses, the threshold was set at α= .001, as per recommendation by Euesden et al. (2015).

Figures 4.5a to **4.5d** show the power calculations for each sample. The results indicate that for the candidate gene analyses, at the α= .05 threshold, there was sufficient statistical power (> 70%) to detect genetic effects of 1% and above in STRATEGIES, 2% and above in TEDS and 3% and above in CogBIAS. At the corrected thresholds, STRATEGIES still had sufficient power to detect the 1.5% effect in VNTR analyses (α= .01), and effect sizes of 2% and above for gene-based analyses (α= .003). TEDS and CogBIAS had less power at the corrected thresholds (< 20%), but were sufficiently powered to detect larger effect sizes of 3% and 5% respectively. Therefore all samples were sufficiently powered to detect the kind of effect sizes reported in previous candidate gene studies (e.g. Chen et al., 2011) but not to detect small effects of .01% to .05%, as would realistically be expected from a single variant.

For genome-wide analyses, at the α= .05 threshold, there was over 70% power in the TEDS-CogBIAS data to detect small effect sizes of .05%. There was over 82% power to detect effect sizes of 1% and larger. TEDS and CogBIAS samples were underpowered to detect the smaller effect sizes (< 30% and 40%), but had sufficient power to detect larger effects of 2% and above and 3% and above respectively. At the corrected thresholds, there was over 70% power in the TEDS-CogBIAS data to detect effect sizes of 3% and above for gene-based and gene-set analysis. All other samples

were underpowered to detect a similar or smaller effect size at this corrected threshold. For polygenic score analyses, there was over 80% power to detect effect sizes of 1.5% and above in the TEDS-CogBIAS sample. The power to detect a similar effect in TEDS and CogBIAS samples was low (< 40% and 20%, respectively), but over 70% in TEDS for effect sizes of 3% and above. All samples were underpowered to detect effect sizes of less than 1% at genome-wide threshold for GWAS analyses.

In summary, the TEDS-CogBIAS sample is sufficiently powered (> 70%) to find the expected effect sizes of 1% and above in polygenic score analyses, and 3% and above in gene-based and gene-set analyses. For candidate gene analyses, STRATEGIES sample was sufficiently powered to detect effect sizes of 1.5% and above, however, it was not sufficiently powered to detect more realistic, smaller effects expected from single variants (< .01%). None of the samples were powered enough to detect the small effect sizes from GWAS, the results of GWAS analyses in the current chapter should therefore be considered exploratory and preliminary.

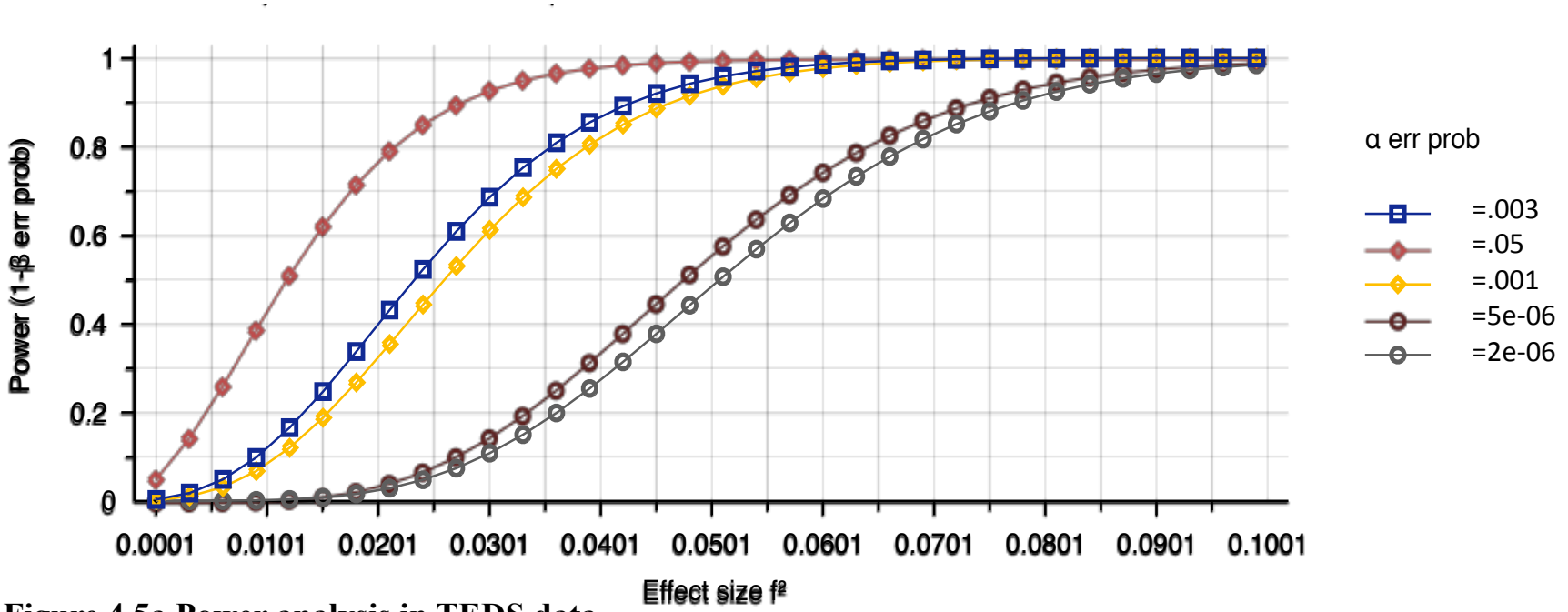


Figure 4.5a Power analysis in TEDS data

Figure shows power analysis for a range of expected effect sizes at various alpha error thresholds including multiple- testing- corrected alphas (gene-based analysis a=2e-06; gene-set analysis a=5e-6; polygenic score analysis a=.001; candidate gene analysis a=.003) and uncorrected a for all analyses=.05. Model parameters: Linear multiple regression, fixed model, R^2 deviation from zero, number of predictors=6, N=642

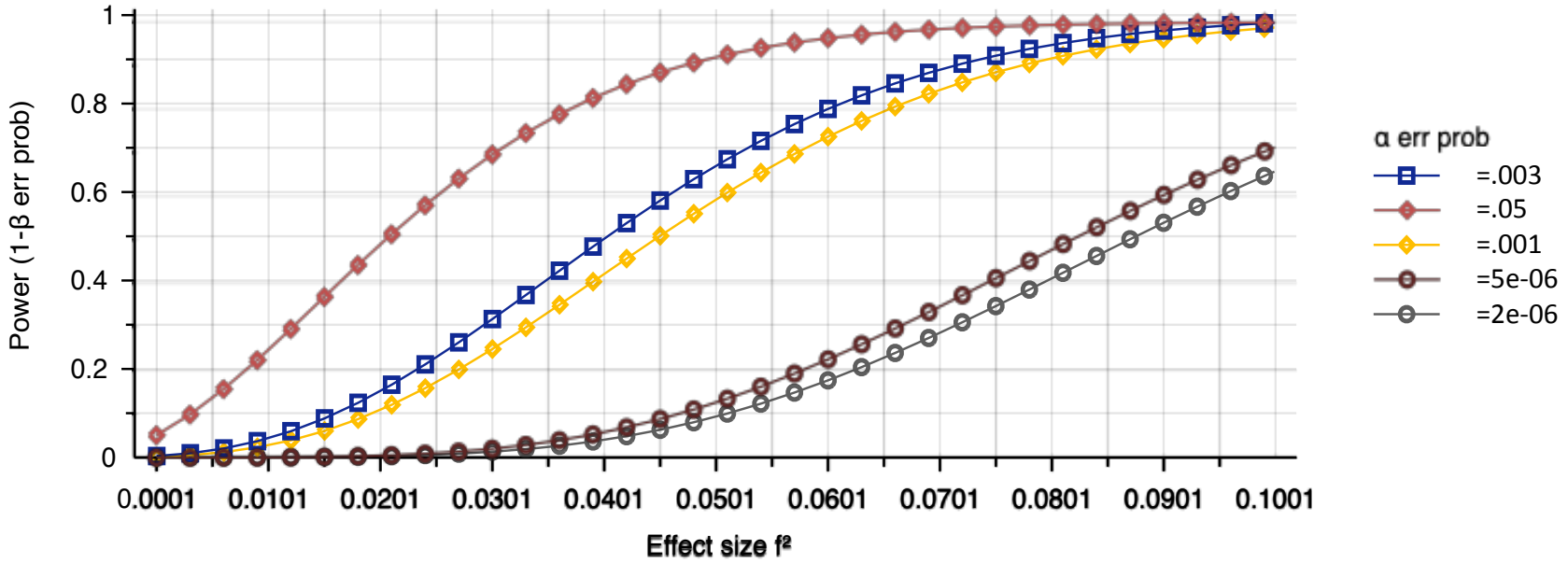


Figure 4.5b Power analysis in CogBIAS data

Figure shows power analysis for a range of expected effect sizes at various alpha error thresholds including multiple-testing- corrected alphas (gene-based analysis a=2e-06; gene-set analysis a=5e-6; polygenic score analysis a=.001; candidate gene analysis a=.003) and uncorrected a for all analyses=.05. Model parameters: Linear multiple regression, fixed model, R^2 deviation from zero, number of predictors=7, N=395

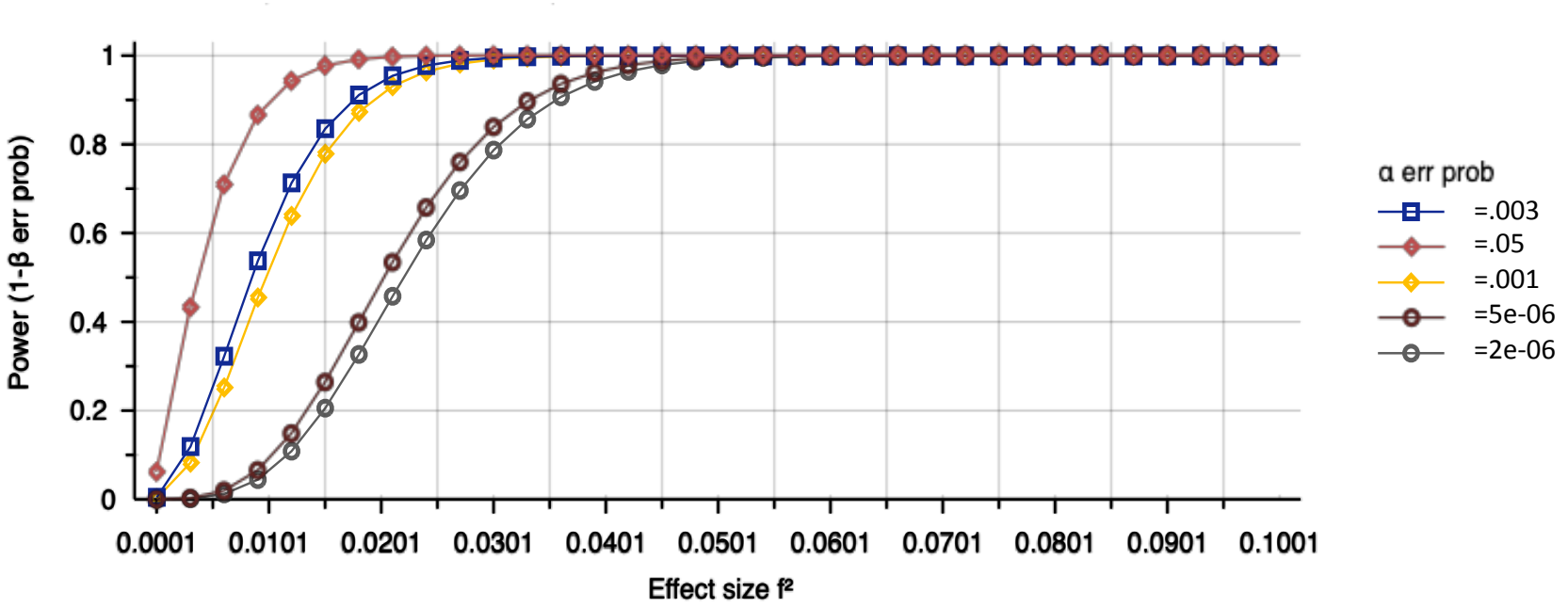


Figure 4.5c Power analysis in meta-analysed TEDS-CogBIAS data

Figure shows power analysis for a range of expected effect sizes at various alpha error thresholds including multiple-testing- corrected alphas (gene-based analysis a=2e-06; gene-set analysis a=5e-6; polygenic score analysis a=.001; candidate gene analysis a=.003) and uncorrected a for all analyses=.05. Model parameters: Linear multiple regression, fixed model, R^2 deviation from zero, N=1035.

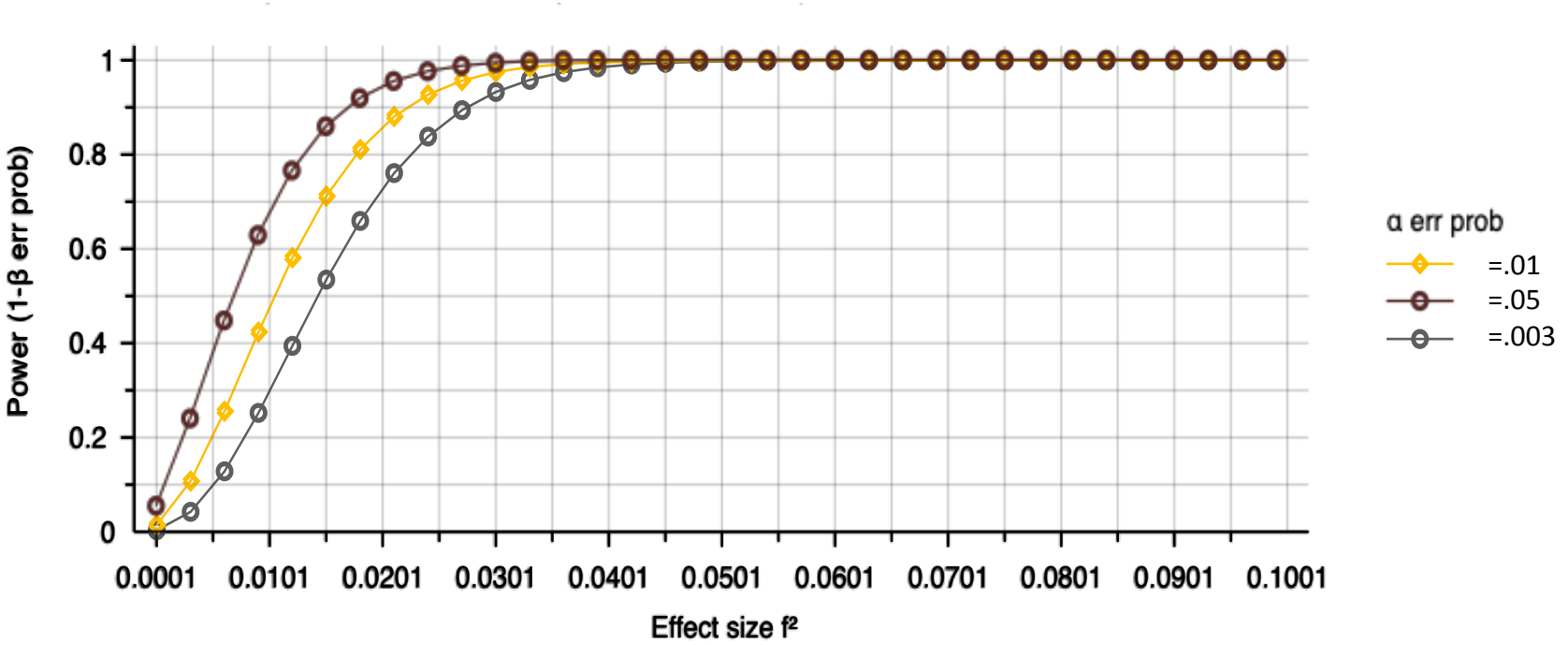


Figure 4.5d Power analysis in STRATEGIES data

Figure shows power analysis for a range of expected effect sizes at various alpha error thresholds including multiple- testing- corrected alphas (VNTR analyses a=.01, candidate gene analysis a=.003) and uncorrected a= . 05. Model parameters: Linear multiple regression, fixed model, R^2 deviation from zero, number of predictors=3, N=838

4.3 Results

The results are presented in two main sections according to candidate gene or genome-wide approaches.

4.3.1 Results: Candidate gene approaches

4.3.1.1 VNTR analysis

The allele frequencies for each VNTR were examined, and the distributions of genotypes in the sample were tested for HWE, using the Hardy Weinberg package in R. The results, as presented in **Table 4.4**, showed no deviation from HWE for the 5 examined VNTRs. For the regression analyses, genotypes for each VNTR were coded in an additive or dominant genetic model for the sensitivity alleles, according to previous studies of these candidate gene (Belsky et al., 2014). This resulted in *DAT1*, *5-HTTLPR* and *STin2* being coded as an additive genetic model (i.e. homozygous for sensitivity allele=2, heterozygous=1, homozygous for the non-sensitivity allele=0) and *MAOA* and *DRD4* as dominant genetic models (i.e. homozygous for sensitivity allele=1, heterozygous=1, homozygous for the non-sensitivity allele=0). **Table 4.5** shows the designated sensitivity alleles and genotype coding. For the additive models, those with individuals with rare alleles (< .01% frequency) were excluded from analysis (*STin2* 9R; 27 individuals), *DAT1* (3, 6, and 11 R; 16 individuals). For *MAOA*, analyses were conducted separately for men and for women. For each linear regression model, sensitivity was the outcome and the VNTR as the predictor, plus age and gender as covariates (expect for *MAOA* where age was the only covariate). As seen in **Table 4.5**, the results did not reveal any significant associations between any of the examined VNTRs and variations in the phenotype of environmental sensitivity. The direction of association was positive for *5-HTTLPR* (β= .04, p= .35) and *MAOA* (β_{Male}=.08, p=.34; β_{Female}=.06, p=.51), such that higher phenotypic sensitivity was associated with higher number/presence of sensitivity alleles. For *DAT1*, *DRD4* and *STin2* however, the direction of association was inverse, such that higher levels of sensitivity were associated with lower number/presence of sensitivity alleles (β= -.04, -.03, -.02; p= .32, .61, .65 respectively).

Table 4.4 Genotype frequencies and Hardy Weinberg test for candidate VNTRs

VNTR	Gene location	Genotype frequencies	*N*	HWE test (p-value)
5-HTTLPR	(17q11.2)	14/14= 0.19 16/16= 0.33 14/16= 0.48	825	X^2= .039 (0.39)
DAT1	(5p15.3)	9/9= 0.07 9/10= 0.36 10/10= 0.55 3/10= 0.002 3/9= 0.001 6/9= 0.001 6/10= 0.004 9/11= 0.005 10/11= 0.006	827	X^2= 1E-3 (0.44)
STin2	(17q11.2)	12/12= 0.39 10/10= 0.14 10/12= 0.45 9/10= 0.02 9/12= 0.01	833	X^2 = 7E-04 (0.23)
DRD4	(11p15.5)	2/3= 0.01 3/4= 0.07 2/4= 0.14 2/7= 0.04 3/7= 0.02 4/7= 0.25 2/2= 0.01 4/4= 0.40 7/7= 0.04 4/8= 0.004 4/6= 0.004 4/5= 0.02	824	X^2= 2E-10 (0.71)
MAOA	(Xp11.23-11.4)	2/0= 0.005 3/0= 0.30 3.5/0= 0.02 4/0= 0.66 5/0= 0.02 3/3.5= 0.01 3/3= 0.11 3/5= 0.01 3.5/4= 0.02 3/4= 0.42 4/5= 0.01 4/4= 0.42	843	X^2= 2E-07 (0.81)

Table 4.5 Association between VNTRs and environmental sensitivity

VNTR	Location	Sensitivity allele	Genotype coding model	*N*	*β*	*S.E.*	*t*	*p-value*
5-HTTLPR	(17q11.2)	Short allele variant	Additive: S/S vs. L/S vs. L/L	825	.04	.04	.94	.35
STin2	(17q11.2)	12 repeat variant	Additive: 10R/10R vs.10R/12R vs. 12R/12R	812	-.02	.04	-.46	.65
DAT1	(5p15.3)	9 repeat variant	Additive: 9R/9R vs.9R/10R vs. 10R/10R	812	-.04	.05	-1.00	.32
DRD4	(11p15.5)	7 repeat variant	Dominant: 7R vs. not 7R	824	-.03	.06	-.52	.61
MAOA	(Xp11.23-11.4)	Low activity variants	Dominant: low activity (0,2,3,5 R) vs. high activity (3.5,4 R)	Female: 406	.06	.08	.67	.51
				Male: 418	.08	.08	.95	.34

4.3.1.2 Candidate gene-based analysis

Gene-based analyses were conducted on the environmental sensitivity candidate genes available in each data set (17 genes in STRATEGIES and 19 in CogBIAS and TEDS), using the multi-model option in MAGMA. Covariates included age, and gender in all datasets, with PCs as additional covariates in TEDS and CogBIAS data. The results identified three significant ($p < .05$) associations in TEDS (*HTR2A*, $p = .02$; *ESR1*, $p = .03$; *COMT*, $p = .03$), but none in CogBIAS and STRATEGIES. The significant associations, however, were not replicated across data sets, nor were the associations significant following Bonferroni correction for multiple testing (.05/19= .003). The full results are presented in **Table 4.6.**

Table 4.6 Results of the candidate gene analyses across three datasets

				TEDS			CogBIAS			STRATEGIES		
GENE	CHR	START	STOP	NSNPS	ZSTAT	*p*	NSNPS	ZSTAT	*p*	NSNPS	ZSTAT	*p*
APOE	19	45389039	45432650	3	-1.03	.85	70	-.24	.59	42	-1.33	.91
BDNF	11	27656440	27763605	57	-1.08	.86	130	1.03	.15	106	1.05	.15
COMT	22	19909263	19977498	52	1.88	**.03**	231	-1.58	.94	190	.79	.21
CREB1	2	208374616	208490284	76	.29	.38	106	-1.25	.89	88	-.78	.78
CRHR1	17	43677710	43933194	780	-.74	.77	1099	.77	.22	578	-.77	.78
DRD2	11	113260317	113366413	152	.52	.30	205	-.93	.82	224	-.56	.71
DRD4	11	617305	660706	6	-.39	.65	132	-.24	.59	92	1.34	.09
ESR1	6	151991631	152444409	488	1.94	**.03**	980	-.67	.75	-	-	-
FKBP5	6	35521362	35716360	178	-2.23	.99	225	-1.38	.92	224	-.14	.56
GABRA2	4	46226470	46412056	238	.38	.35	284	.77	.22	284	-1.13	.87
HTR1A	5	63235875	63278119	28	-.77	.78	53	-.40	.65	30	-.61	.73
HTR2A	13	47385677	47491211	149	2.17	**.02**	265	-.04	.51	251	.14	.44
NR3C1	5	142637496	143133322	561	-.80	.79	917	.97	.17	178	.59	.28
OXTR	3	8772094	8831300	53	-1.54	.94	181	-.57	.72	228	-1.03	.85
SIRT1	10	69624427	69698147	64	.32	.38	127	-1.26	.90	-	-	-
SLC6A3	5	1372905	1465543	63	.02	.49	56	-.13	.55	276	-.70	.76
SLC6A4	17	28501337	28582986	47	.25	.40	89	1.29	.10	78	.29	.39
TPH1	11	18022084	18082354	39	1.19	.12	99	.86	.20	93	1.33	.09
TPH2	12	72312626	72446221	234	.28	.39	310	.66	.25	259	1.22	.11

START/STOP: the annotation boundaries of the gene on that chromosome (window=20); NSNPS: the number of SNPs annotated to that gene that were found in the data; ZSTAT: Z statistic of the gene, a measure of the strength of association between the trait and the gene; *p:* the gene p-value (uncorrected for multiple testing); *N*=641 (TEDS), 394 (CogBIAS), 838 (STRATEGIES); Bonferroni corrected p-value=0.003 (.05/19); associations with uncorrected $p < .05$ are in bold

4.3.2 Results: genome-wide approaches

4.3.2.1 GWAS analyses

GWAS was conducted separately on TEDS and CogBIAS datasets, which included 642 individuals and 3,220,761 SNPs in TEDS and 5,595,637 variants and 395 individuals in CogBIAS. PLINK was used to run a linear regression, in an additive genetic model, with sensitivity as the outcome, and age, gender and PCs (3 CogBIAS, 4 TEDS) as covariates in the model. Genomic inflation was calculated based on median chi-square p-values and empirical p-values were obtained via 1000 permutations. The genome-wide significance threshold was set at $5x10^{-8}$. As would be expected from the small sample sizes, there were no genome-wide significant SNPs identified in either data set. The top SNP in TEDS (p= 2.4E-06) was rs4918121 located on Chromosome 10, in the intergenic region of the Sortilin-Related VPS10 Domain Containing Receptor 3 (*SORCS3*) gene. *SORCS3* is a protein -coding gene, where it encodes a type-I receptor transmembrane protein. The transcript is expressed at high levels in the brain and adrenal gland (Fagerberg et al., 2014) and variations in this gene have been associated with Alzheimer disease and multiple sclerosis in candidate gene studies (Binzer et al., 2016; Reitz et al., 2013). The SNP was not found in the GWAS catalog. This SNP was tagged in the CogBIAS data, and while the association was in the same direction, its p-value was not significant (p= 0.57).

The top SNP in CogBIAS (p= 1.5E-07) was rs6435333 located on chromosome 2, in the intronic region of the Potassium Voltage-Gated Channel Subfamily J Member 3 (*KCNJ3*) gene. The protein encoded by this gene is an integral membrane protein and inward-rectifier type potassium channel. The encoded protein is controlled by G-proteins and plays an important role in regulating heartbeat.

The SNP was not in the GWAS catalogue and was not tagged in the TEDS data. The top 20 SNPs in each dataset, as well as the Manhattan plots and the QQ plots of the p-values for each data set are presented in **Appendix 4.1**.

4.3.2.2 Meta-analysis of GWAS results

The GWAS results of harmonized TEDS and CogBIAS data (2,545,244 SNPs**)** were meta-analysed using the Standard Error option in METAL (Willer et al., 2010), as well as the additional options of testing for heterogeneity effects across samples and applying genomic control correction to the p-values. The METAL heterogeneity analysis determines whether observed effect sizes (or test statistics) are homogeneous across samples.

The results of the meta-analysis indicated that there were no genome-wide significant findings. The heterogeneity analysis identified 123,111 SNPs as showing significant heterogeneity effects across samples, with 119,576 SNPs having differences in the direction of effect and 3,544 showing differences in the magnitude of the effect. The Manhattan plot and QQ plot of the p-values are presented in **Figure 4.6a** and **4.6b.** The top 20 SNPs from the meta-analysis are presented in **Table 4.7.** The top SNP from the meta-analysis was rs17121012, located on Chromosome 1, in the intronic region of the uncharacterized *LOC101926964* gene. Although the specific function of this gene is as yet unknown, this is a long non-coding RNA gene (lncRNAs), with this class of gene emerging as important players in regulation of gene expression in higher eukaryotes. Recent studies have found variations in lncRNAs genes to be relevant to a range of cancers such as Pancreatic Ductal Adenocarcinoma (Song et al., 2018).

Table 4.7 Top 20 SNPs from the meta-analysis of TEDS and CogBIAS GWAS

SNP	A1	A2	A1 Freq	Freq SE	*B*	*S. E*	*p*	Direction
rs17121012	A	T	.90	.01	.32	0.07	1.1E-06	++
rs2885689	C	G	.90	.01	.32	0.07	1.3E-06	++
rs742277	T	C	.69	.01	.21	0.04	1.6E-06	++
rs2867896	T	C	.32	.01	-.20	0.04	2.6E-06	--
rs73621982	C	G	.69	.01	.20	0.04	3.0E-06	++
rs16987740	A	G	.69	.01	.20	0.04	3.0E-06	++
rs66633066	T	C	.69	.01	.20	0.04	3.0E-06	++
rs3764701	A	T	.69	.01	.20	0.04	3.1E-06	++
rs4812349	T	C	.31	.01	-.20	0.04	3.1E-06	--
rs8121775	A	G	.69	.01	.20	0.04	3.1E-06	++
rs4812350	T	C	.31	.01	-.20	0.04	3.5E-06	--
rs2179318	T	C	.68	.01	.20	0.04	3.5E-06	++
rs7267954	A	G	.31	.01	-.20	0.04	4.0E-06	--
rs2092261	A	G	.69	.01	.20	0.04	4.3E-06	++
rs3752299	A	G	.69	.01	.20	0.04	4.3E-06	++
rs3764703	T	C	.69	.01	.20	0.04	4.3E-06	++
rs2867895	T	C	.69	.01	.20	0.04	4.4E-06	++
rs8118861	T	C	.69	.01	.20	0.04	4.4E-06	++
rs4812345	T	C	.31	.01	-.20	0.04	4.7E-06	--
rs6028233	T	C	.31	.01	-.20	0.04	4.7E-06	--

A1=Minor Allele, A2=Major Allele, A1Freq= A1 allele frequency across datasets, Freq SE=Standard error of A1 allele frequency; *B*=meta-analysed Beta; *S.E*= Standard Error; P= p-value; direction of effect across data sets

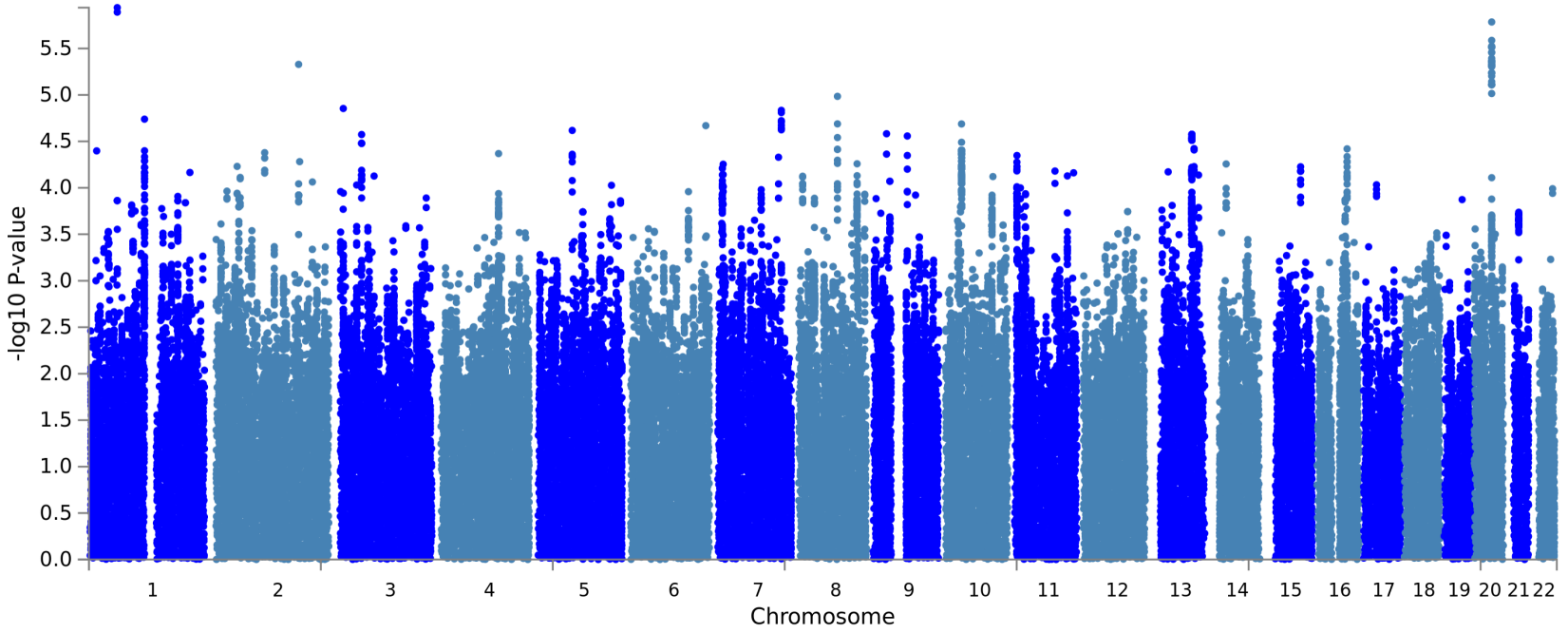


Figure 4.6a Manhattan plot of the meta-analysed TEDS-CogBIAS GWAS

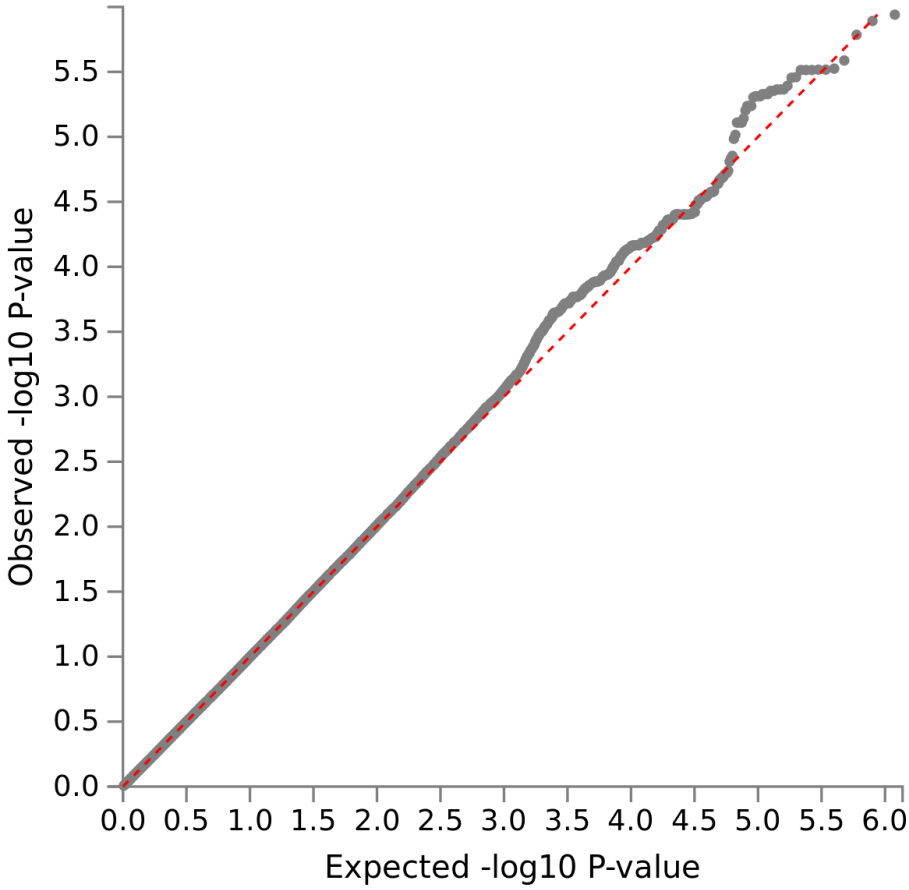


Figure 4.6b Q-Q plot of the meta-analysed TEDS-CogBIAS GWAS

Lead and independent significant SNPs from the GWAS results were identified. Independent significant SNPs were defined as those with p < 1E-5 which were independent from each other with r^2>.6. These SNPs are essentially the SNPs that are contained after clumping GWAS tagged SNPs at the same p-value and r^2. Lead SNPs were defined as independent significant SNPs, which were independent from each other at $r^2 < 0.1$. Therefore, lead SNPs are same as the SNPs clumped independent significant SNPs at p < 1E-5 and $r^2 < 0.1$.

Three lead SNPs were identified, which included the top SNP rs17121012, as well as rs6726395 (p=4.7E-06) located on chromosome 2 in the intronic region of the NF-E2-Related Factor 2 (*NFE2L2*) gene, and rs742277 (p=1.6E-06) located on Chromosome 20, in the intronic region of the DEAH-box helicase 35 (*DHX35*) gene. *NFE2L2* gene encodes a transcription factor, which is involved in regulation of genes involved in response to injury and inflammation and oxidative stress. *DHX35* is a protein-encoding gene, with its protein implicated in a number of cellular processes involving alteration of RNA secondary structure. While the exact function of this protein is unknown, other proteins in this family are believed to be involved in embryogenesis, spermatogenesis, and cellular growth and division. None of these SNPs were found in GWAS catalogue and they were not within or close to any of the genes previously implicated in differential susceptibility from candidate-gene approaches. **Figures 4.7a, 7b** and **4.7c** show the genomic region for these 3 SNPs.

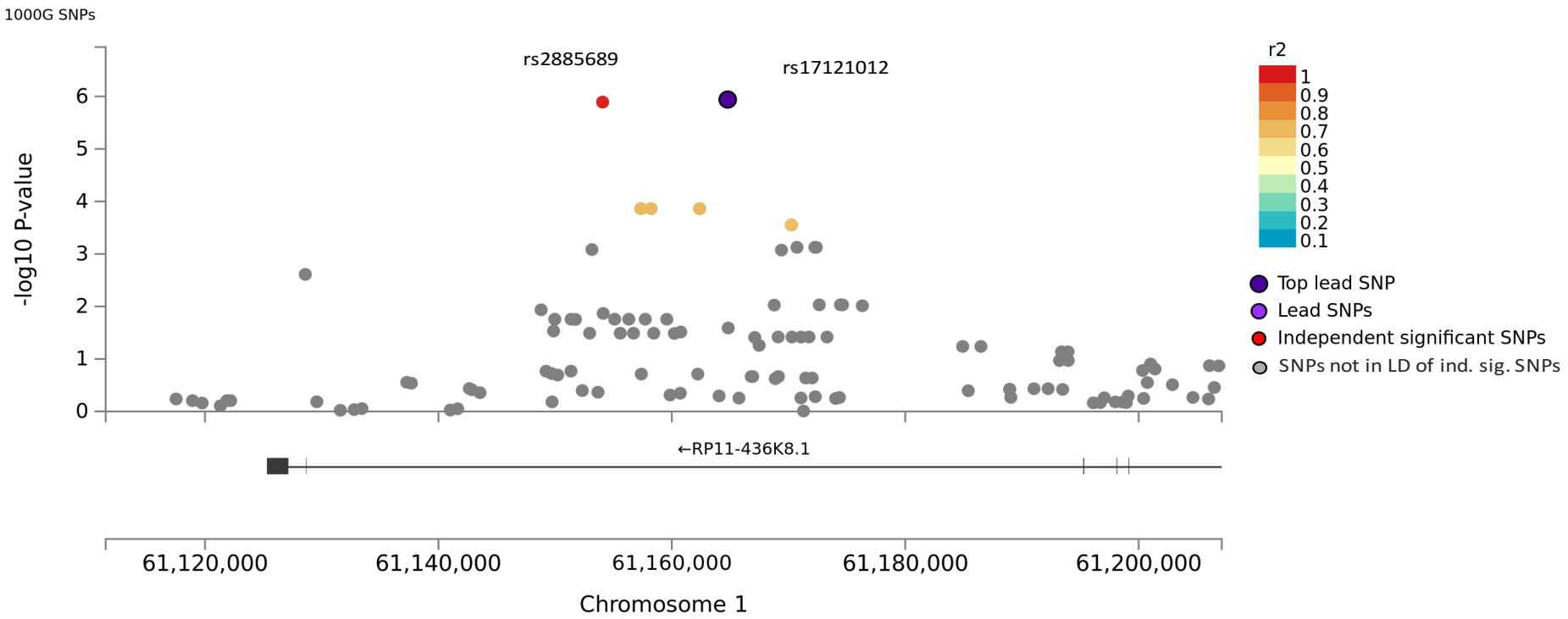


Figure 4.7a Genomic region plot for top significant lead SNP (rs17121012) from meta-analysed GWAS results

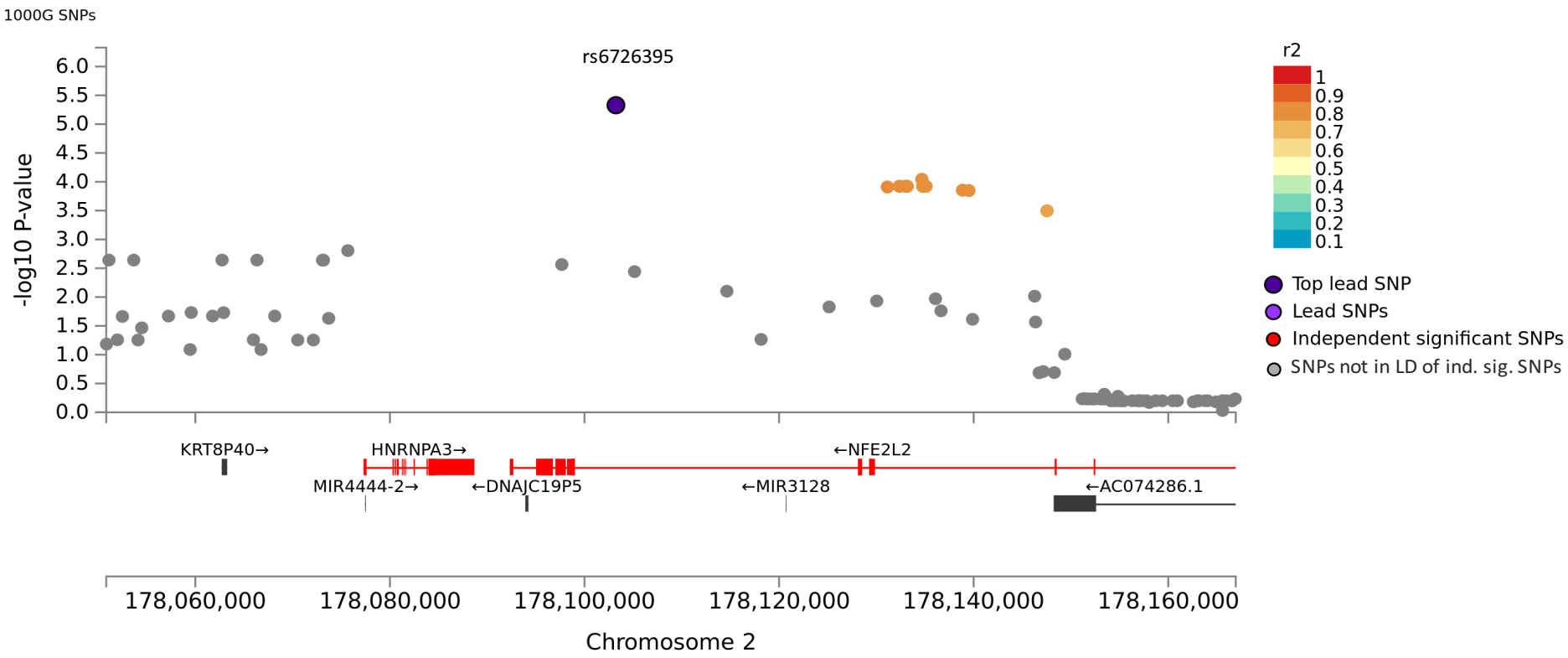


Figure 4.7b Genomic region plot for top significant lead SNP (rs6726395) from meta-analysed GWAS results

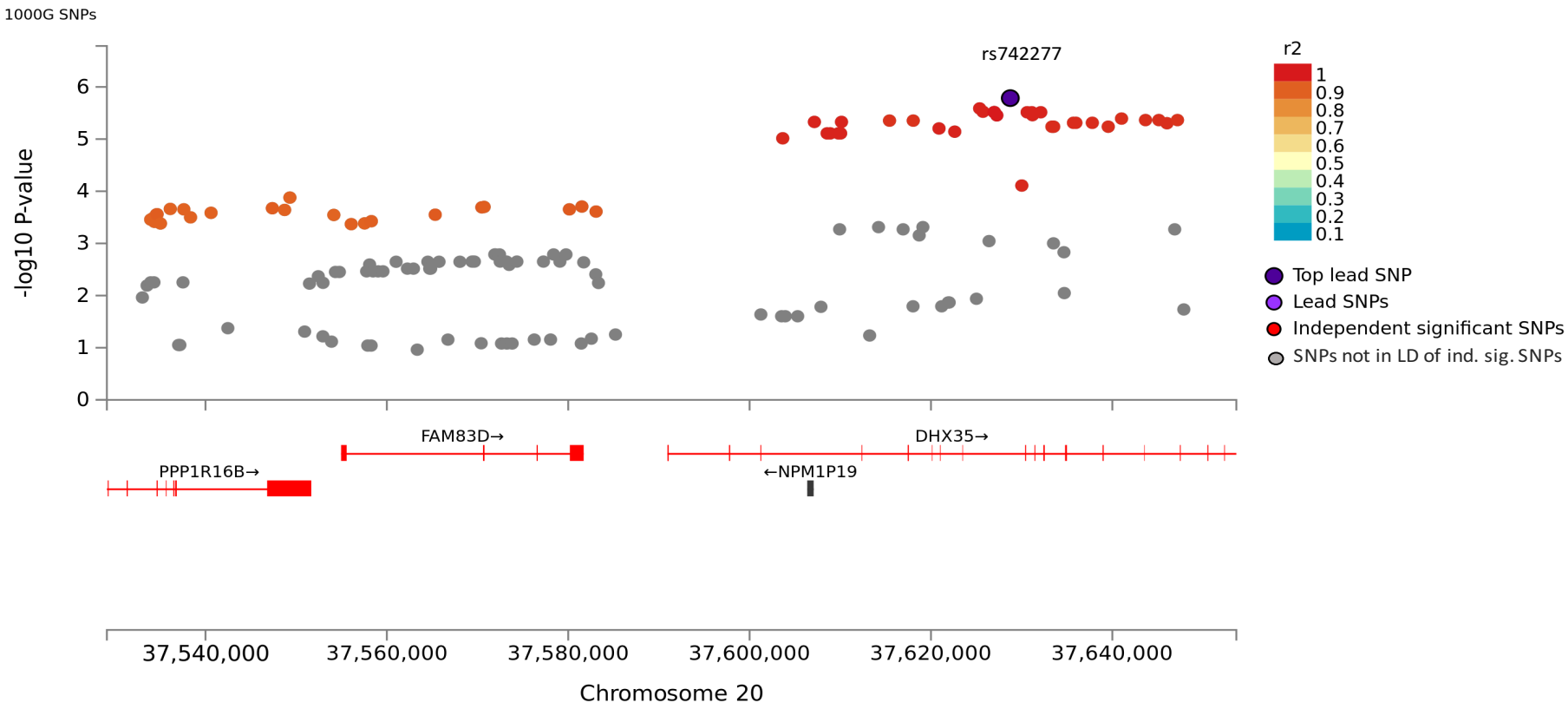


Figure 4.7c Genomic region plot for top significant lead SNP (rs74227) from meta-analysed GWAS results

4.3.2.3 Gene-based analyses

SNPs in TEDS, CogBIAS and meta-analysed CogBIAS-TEDS datasets were annotated to functional genes from the NCBI build 37. There were 18,094 genes in CogBIAS, 18,089 genes in TEDS. The multi-model option of MAGMA was used for gene-based analyses, this model controls for number of samples and minor allele count (MAC) in the resultant gene statistics. The linear regression model to examine the association between sensitivity and genes included sex, gender and PCs (4 CogBIAS and 3 TEDS) as covariates.

While the analyses identified many genes with $p < .05$ in both TEDS and CogBIAS data, these associations were not robust to Bonferroni correction for multiple testing p-value threshold (p= 2.8E-06), except for one gene in TEDS data (p=1.7E-06), Ladybird Homeobox 1 (*LBX1*) in Chromosome 10. *LBX1* is a protein-coding gene, with its homeobox transcription factor being involved in spinal cord differentiation and somatosensory signal transduction (Xu et al., 2012). Polymorphisms in this gene have been associated with risk for adolescent idiopathic scoliosis in recent genetic association studies (Cao, Min, Zhang, Li, & Li, 2016). This gene has not been previously studied as a differential susceptibility candidate gene. The association between this gene and sensitivity was not significant in CogBIAS data (p= .19).

The top gene in the CogBIAS (p= 1.1E-05) was Cytochrome P450 Family 2 Subfamily B Member 6 (*CYP2B6*), a protein coding gene in Chromosome 19, which encodes a member of the cytochrome P450 superfamily of enzyme. Cytochrome P450 proteins catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The enzyme has been reported to be involved in metabolisms of a range of drugs and is expressed highly in the liver (Pearce et al., 2016). This gene has not been previously studied as a differential susceptibility candidate gene, and the association between this gene and sensitivity was not significant in TEDS (p= .34).

Meta-analysis of the gene-based results, indicated that *LBX1* was the top gene associated with sensitivity across samples (p= 1.4E-05), however, this association was not significant at Bonferroni multiple testing correction threshold (p= 2.8E-06).

The results of the meta-analysis on gene-based results from TEDS and CogBIAS data are presented in **Table 4.8.**

Table 4.8 Top ten genes associated with sensitivity from meta-analysed gene-based results and their associations in the original datasets

	Meta-analysed gene results						Genes in TEDS			Genes in CogBIAS		
GENE	CHR	START	STOP	NSNPS	ZSTAT	*p*	NSNPS	ZSTAT	*p*	NSNPS	ZSTAT	*p*
LBX1	10	102966733	103009954	28	4.20	**1.4E-05**	8	4.64	**1.7E-06***	48	.88	1.9E-01
N4BP3	5	177520556	177573107	45	3.89	**5.0E-05**	4	2.58	**4.9E-03**	85	3.01	**1.3E-03**
OR56A3	11	5948577	5989524	88	3.86	**5.8E-05**	48	1.93	**2.7E-02**	127	3.79	**7.5E-05**
NHP2	5	177556464	177600961	37	3.72	**9.8E-05**	7	2.537	**5.6E-03**	67	2.80	**2.6E-03**
EHD3	2	31436880	31511260	146	3.69	**1.1E-04**	80	2.48	**6.6E-03**	212	2.82	**2.4E-03**
LOC100130880	7	137618094	137662712	57	3.60	**1.6E-04**	40	4.02	**2.9E-05**	73	.70	2.4E-01
NXPE2	11	114529200	114599357	148	3.58	**1.7E-04**	119	2.29	**1.1E-02**	176	2.89	**2.0E-03**
DHX35	20	37570981	37688366	140	3.58	**1.7E-04**	110	3.78	**7.8E-05**	169	.97	1.7E-01
TSHR	14	81401333	81632646	519	3.55	**1.9E-04**	398	2.84	**2.3E-03**	640	2.13	**1.7E-02**
NFE2L2	2	178075031	178149859	65	3.53	**2.0E-04**	30	3.66	**1.3E-04**	99	1.06	1.4E-01

*Associations with p-value significant at Bonferroni correction threshold; Associations with $p < .05$ are in bold; START/STOP: the annotation boundaries of the gene on that chromosome (window=20); NSNPS: the number of SNPs annotated to that gene that were found in the data; ZSTAT: Z statistic of the gene, a measure of the strength of association between the trait and the gene; *p:* the gene p-value (uncorrected for multiple testing)

4.3.2.4 Gene-set analyses

Gene-set analyses: Genes in TEDS, CogBIAS and meta-analysed data were annotated to 10,648 gene-sets obtained from Broad Institute MsigDB v5.2 (Subramanian et al., 2005). There were 10,644 gene-sets in TEDS and CogBIAS.

The results revealed many significant ($p < .05$) gene-sets in both TEDS and CogBIAS. Only one gene-set, PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY, was found to be significant at Bonferroni multiple testing correction threshold (p = 4.8E-06), in TEDS. This gene-set was not significant in CogBIAS (p= .12).

The significant gene-set was from Gene-Onthology (GO) and included 59 genes in TEDS, with 7 genes (CDC14B, CDC14B, PPM1L, PPM1L, CYCS, PPP2R5D, PDP2) showing p-values < .05 within this gene- set (see **Table 4.9**). The genes in this gene-set reflect the serine/threonine phosphatase pathway activity. Protein serine/threonine phosphatase is a form of phosphoprotein phosphatase that can to reverse the addition of serine/threonine protein kinases enzymes to phosphate serine/threonine amino acids. The addition and removal of phosphate groups regulates many cellular mechanisms including cell differentiation, protein synthesis, apoptosis (programmed cell death) and embryonic development (Shi, 2009).

For the meta-analysis of the gene-sets, meta-analysed gene-based results were used to obtain evidence of association with sensitivity across the two datasets. The results of the top 10 gene-sets are presented in **Table 4.10**.

As was expected from the non-significant association in CogBIAS, the PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY gene-set was not in the top ten significant gene-sets. The top gene-set (p= 7.6E-05), MIKKELSEN_ES_ICP_WITH_H3K4ME3_AND_H3K27ME3, included 135 genes with intermediate-CpG-density promoters (ICP) bearing bivalent histone H3 methylation mark (H3K4me3 and H3K27me3) in embryonic stem cells (Mikkelsen et al., 2007). Genes in this gene-set are therefore relevant to expression and regulation of embryonic stem cells and subsequently a large range of processes involved in human development. The association for this gene-set was significant in both TEDS (p= 4.5E-03) and CogBIAS (p= 5.7E-02) data. This gene-set however did not surpass the Bonferroni multiple testing corrected threshold (p= 4.8E-06).

Table 4.9 Top 20 genes from the significant gene-set (PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY) in TEDS data

GENE	CHR	START	STOP	NSNPS	ZSTAT	*p*
CDC14B	9	99232807	99402112	63	3.47	**2.6E-04**
DUSP23	1	159730730	159772333	35	2.69	**3.5E-03**
PPM1L	3	160453996	160808817	435	2.63	**4.2E-03**
CYCS	7	25138270	25184980	73	2.45	**7.1E-03**
PPP2R5D	6	42932218	43000083	80	2.43	**7.6E-03**
PDP2	16	66894360	66945004	21	2.05	**2.0E-02**
CDC14A	1	100790598	101005833	146	1.61	**5.4E-02**
PPP1R15B	1	204349781	204400945	20	1.39	8.3E-02
LCK	1	32696840	32771766	14	1.36	8.7E-02
MYH6	14	23829942	23898836	55	1.20	.11
RPAP2	1	92744522	92873732	71	1.16	.12
PPA2	4	106270234	106415227	321	1.09	.14
MTMR14	3	9671117	9764078	41	1.08	.14
CDKN3	14	54843657	54906936	48	1.04	.15
PPM1M	3	52259782	52304615	34	1.00	.16
CTDSP1	2	219243061	219290664	7	.99	.16
PPEF2	4	76761025	76843681	71	.92	.18
CTDSP2	12	58193710	58260747	30	.89	.19
PP2D1	3	20001453	20073765	67	.87	.19
SSU72	1	1457053	1530262	18	.82	.21

$p < .05$ are in bold

Table 4.10 Top ten gene-sets from meta-analysed gene results and their associations in TEDS and CogBIAS data

Gene-set	meta-analysed results						TEDS				CogBIAS			
	N	*B*	St. *B*	*SE*	p_1	p_2	*N*	St. *B*	*SE*	p_1	*N*	St. *B*	*SE*	p_1
MIKKELSEN_ES_ICP_WITH_H3K4ME3_AND_H3K27ME3	135	.25	.02	.07	**7.6E-05**	**3.1E-03**	131	.02	**4.5E-03**	**7.3E-04**	134	.01	**5.7E-02**	.34
GO_PHOSPHATASE_COMPLEX	44	.41	.02	.11	**8.0E-05**	**4.4E-04**	44	.02	**1.5E-04**	**2.6E-04**	44	.01	**2.8E-02**	.17
GO_TRANSLATIONAL_INITIATION	135	.24	.02	.06	**9.0E-05**	9.2E-02	130	.02	**2.0E-03**	**1.2E-02**	134	.01	**8.6E-03**	.75
GO_MODULATION_BY_HOST_OF_VIRAL_PROCESS	18	.61	.02	.17	**1.5E-04**	**1.2E-03**	18	.01	**8.0E-03**	**1.0E-02**	18	.01	**2.8E-02**	.03
SAKAI_TUMOR_INFILTRATING_MONOCYTES_DN	79	.29	.02	.08	**1.6E-04**	9.9E-02	79	.02	**1.2E-03**	**1.0E-02**	78	.01	1.0E-01	.78
GO_REGULATION_OF_CELL_KILLING	62	.34	.02	.10	**2.0E-04**	1.0E-01	61	.01	**5.2E-02**	1.3E-01	62	.01	**1.4E-02**	.28
TSAI_DNAJB4_TARGETS_DN	6	1.14	.02	.32	**2.1E-04**	**1.1E-02**	6	.02	**1.8E-03**	**1.0E-02**	6	.01	**5.7E-02**	.18
BREDEMEYER_RAG_SIGNALING_NOT_VIA_ATM_DN	55	.37	.02	.11	**3.0E-04**	**2.0E-02**	53	.02	**2.1E-03**	**3.0E-02**	55	.01	**1.2E-02**	.16
GO_GDP_DISSOCIATION_INHIBITOR_ACTIVITY	10	.84	.02	.25	**3.2E-04**	1.5E-01	10	.02	**1.7E-03**	**4.0E-02**	9	.01	2.0E-01	.76
GO_REGULATION_OF_NATURAL_KILLER_CELL_MEDIATED_IMMUNITY	34	.42	.02	.12	**3.6E-04**	**5.5E-02**	34	.01	**1.1E-02**	6.0E-02	34	.01	**3.4E-02**	.29

N= Number of genes in the gene-set; *B*= Beta; *SE*=Standard error; St. *B* =Standardized Beta; p_1= gene-set p-value for the competitive model; p_2= gene-set p-value for the self-contained model; associations with $p < .05$ are in bold; Bonferroni correction p-value threshold = 4.8E-06

4.3.2.5 TEDS Polygenic score of sensitivity in CogBIAS

Polygenic scores were constructed from genome-wide SNP data of individuals in CogBIAS, using summary statistics from the GWAS of sensitivity in TEDS, at nine p-value thresholds (P_T= .001, .01, .05, .10, .20, .30, .40, .50, 1), as well as high resolution scoring. Default clumping options in PRSice were used, as described in **Section 4.2.2.4.** There were 2,545,244overlapping variants in the two samples which reduced 74,746 following clumping. Age, sex and 4 PCs were included as covariates in the regression model predicting sensitivity in CogBIAS. There were no significant associations at the specified thresholds, though the high-resolution polygenic scoring identified P_T = .0006 as the best threshold, with the PGS score predicting 1.1% (p= .03) of the variance in sensitivity in CogBIAS. The direction of effect was inverse for the significant PGS, such that a high polygenic score of sensitivity was associated with a low phenotypic sensitivity. These findings may reflect the differences in sample characteristics, or may be spurious due to the small sample size of both target and discovery sample, especially since the beta value flips around after this association to be in the opposite direction, with only 211 SNPs at this threshold.

Table 4.11 shows the proportion of variance explained and number of SNPs at each threshold (including the best score), as well as the relevant p-values. **Figure 4.8** shows the results of the high-resolution polygenic scoring and the bar chart for specified thresholds.

Table 4.11 TEDS Polygenic score of sensitivity in CogBIAS

P_T	N SNPs	Coefficient	Standard Error	R^2	*p*-value
.001	319	-14.49	11.38	.004	.20
.01	2628	-6.94	38.26	.000	.86
.05	10008	-2.25	84.45	.000	.98
.1	17519	34.94	124.23	.000	.78
.2	29459	85.69	175.53	.001	.63
.3	39156	136.11	218.14	.001	.53
.4	47485	136.57	253.76	.001	.59
.5	54531	126.45	284.33	.000	.66
1	74746	227.48	381.32	.001	.55
0.0006*	**211**	**-19.16**	**8.84**	**.011**	**.03**

* Best score from high resolution scoring; associations with $p < .05$ are shown in bold

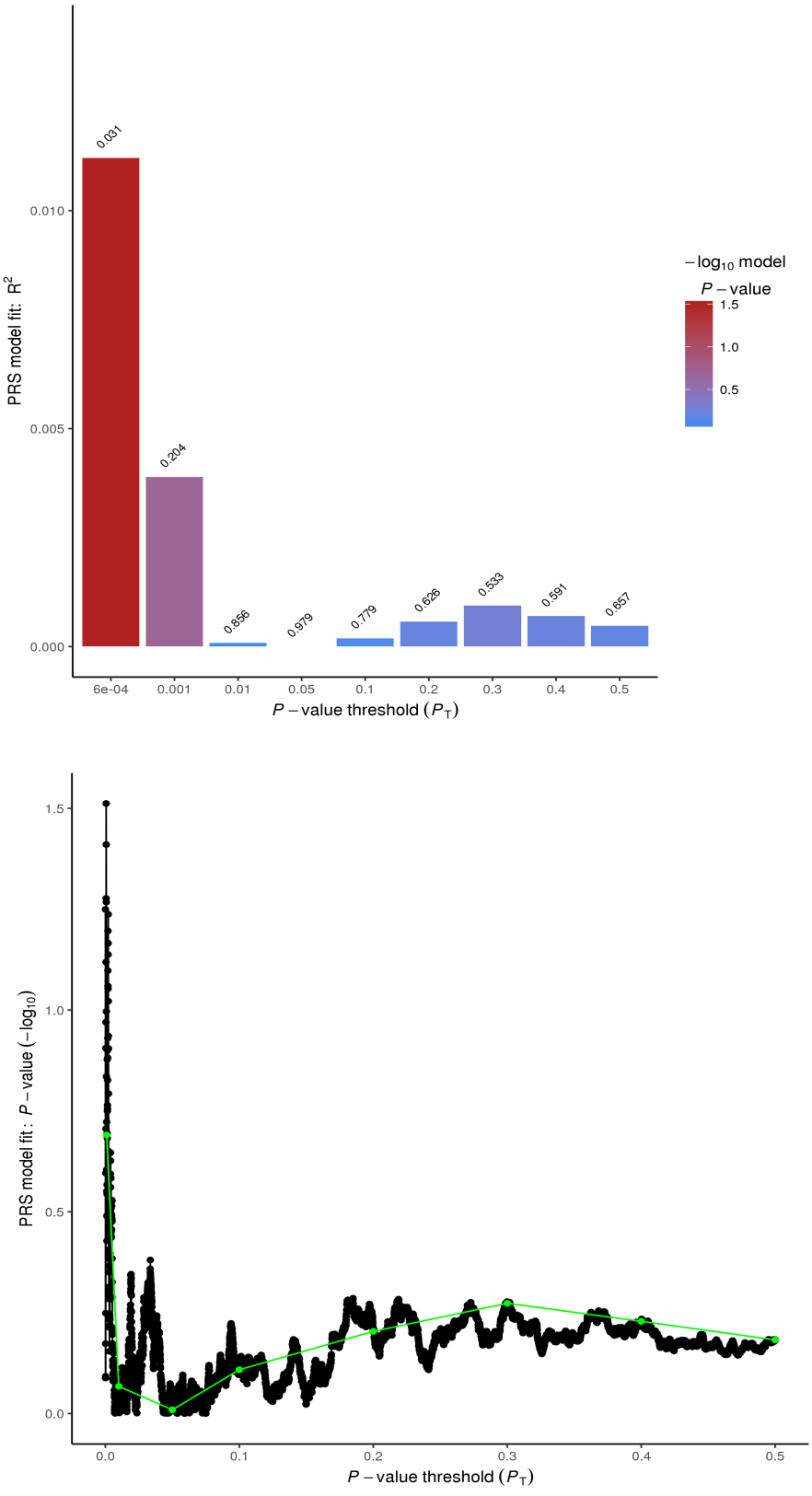


Figure 4.8 TEDS polygenic score of environmental sensitivity in CogBIAS

4.3.2.6 Polygenic score of differential susceptibility

Polygenic scores were constructed in CogBIAS data, based on summary statistics from Keers et al. (2016), at nine p-value thresholds (P_T= .001, .01, .05, .10, .20, .30, .40, .50, 1), as well as high resolution scoring. Default clumping options in PRSice were used as described in **Section 4.2.2.4**. There were 70,464 clumps formed from 509,607 top variants. Age, sex and 4 PCs were included as covariates in the regression model predicting sensitivity in CogBIAS.

The results did not suggest that there was a significant relationship between the polygenic score of differential susceptibility and sensitivity in the CogBIAS sample, though the high-resolution scoring identified a marginally significant (p= .07) effect for best score, predicting .09% of the variance in sensitivity (see **Figure 4.9**). The direction of the effect was positive such that higher PGS scores were associated with higher levels of sensitivity, though there were only 53 SNPs at this threshold, and the beta values flipped around after this threshold. The association is therefore not very robust and may be spurious. **Table 4.12** shows the proportion of variance explained and number of SNPs at the nine p-value thresholds, as well as the relevant p-values, R^2, coefficients and standard errors from the regression models.

Table 4.12 Polygenic score of differential susceptibility predicting environmental sensitivity in CogBIAS

P_T	N SNPs	*B*	Standard Error	R^2	*p*-value
.001	294	10.43	12.66	.002	.41
.01	2220	-11.59	43.30	.000	.79
.05	8837	-137.06	106.13	.004	.20
.1	15618	-220.38	150.72	.005	.14
.2	26698	-290.93	217.77	.005	.18
.3	36000	-354.13	268.54	.004	.19
.4	43756	-474.75	315.33	.006	.13
.5	50506	-494.44	356.45	.005	.17
1	70464	-712.42	493.17	.005	.15
.00015*	53	9.23	5.02	.009	.07

* Best score from high resolution scoring; B= beta-coefficient; R^2 = proportion of variance explained by the polygenic score.

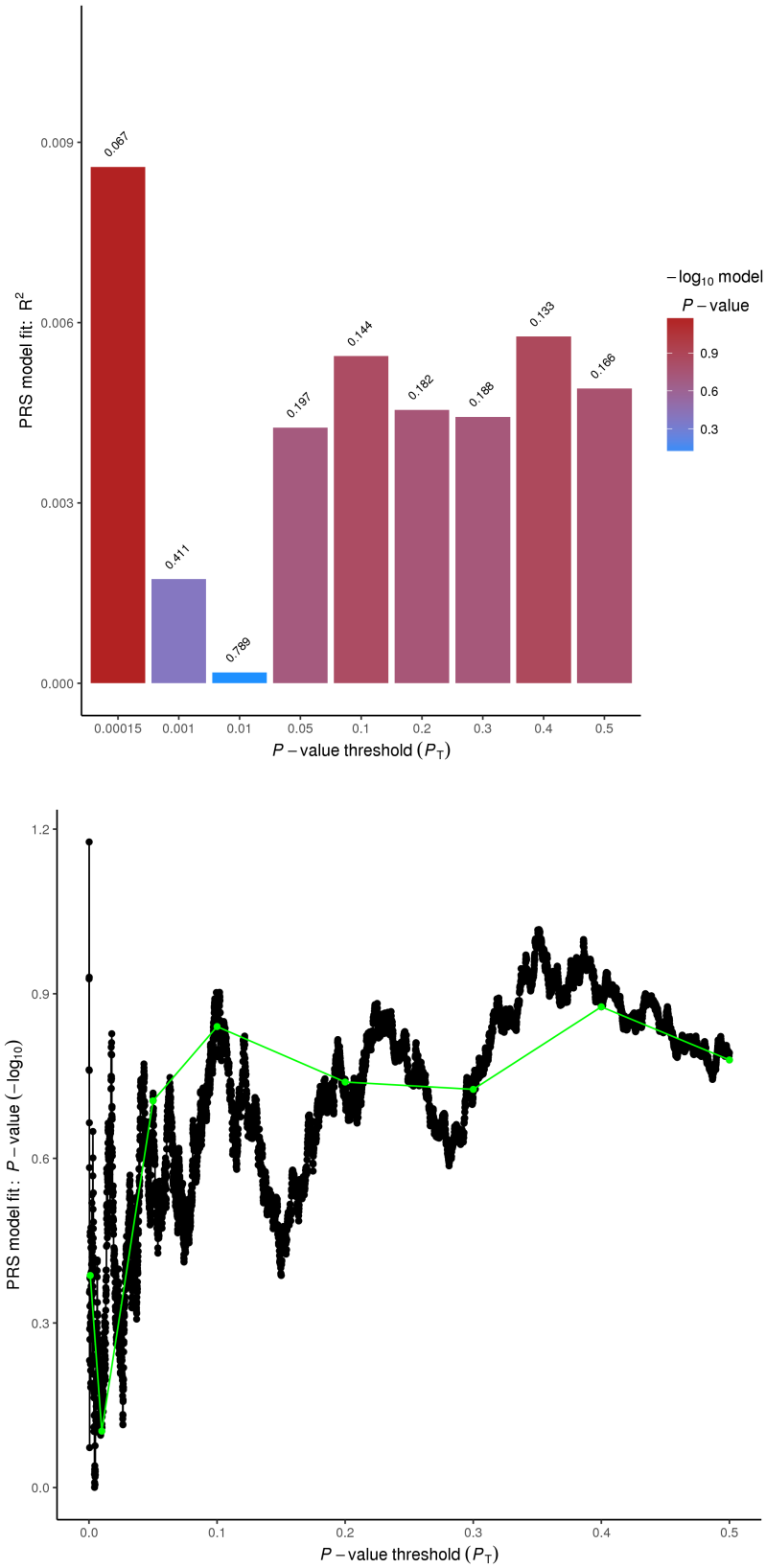


Figure 4.9 Polygenic score of differential susceptibility predicting environmental sensitivity in CogBIAS

4.3.2.7 Cross-trait polygenic score analyses

For the polygenic score analyses, the summary statistics from thirteen publically available GWASs (neuroticism, extraversion, openness, conscientiousness, agreeableness, autism, ADHD, anxiety, depression, insomnia, loneliness, subjective wellbeing, educational attainment) were used to construct PGS from the SNP-data in TEDS and CogBIAS and predict sensitivity in these datasets. The PRSice options for clumping and p-value thresholds were as described in **Section 4.2.2.4**. Age, sex and PCs (3 TEDS, 4 CogBIAS) were included as covariates in the regression model predicting sensitivity. For the sum-sum score analyses, the summary statistics from the meta-analysed GWAS of sensitivity (TEDS-CogBIAS data) were used as the target dataset, after excluding SNPs that showed high heterogeneity across samples. The summary statistics from 13 GWAS data were used as the base data set. The PRSice options for clumping and p-value thresholds were as described in **Section 4.2.2.4**.

The results from **TEDS** data showed significant associations between environmental sensitivity and all personality traits except for neuroticism. The largest association was found for polygenic scores of openness (R^2= 2.5%, p= 4.8E-05), followed by extraversion (R^2= 1.2%, p= 4.9E-03), agreeableness (R^2= 1%, p= 1.1E-02), and conscientiousness (R^2= .7%, p= 3.2E-02). Of psychopathological outcomes, the strongest predictor of sensitivity was autism (R^2= 1.6%, p= 9.6E-04), followed by anxiety (R^2= .9%, p= 1.6E-02), ADHD (R^2= .7%, p= 2.8E-02), Loneliness (R^2= .7%, p= 3.0E-02), and depression (R^2= .6%, p= 4.2E-02). Of the more positive outcomes, subjective wellbeing polygenic score was a significant predictor of sensitivity (R^2= .9%, p= 1.5E-02), and so was educational attainment (R^2= .7%, p=3.2E-02).. No significant associations were found between sensitivity and polygenic scores of neuroticism or insomnia.

The results from TEDS were replicated in **CogBIAS** data for most traits. Of the personality traits, there were significant associations between sensitivity and polygenic scores of openness (R^2= 1.8%, p= 6.8E-03), and extraversion (R^2= 3.1%, p= 3.4E-04). Contrary to TEDS, there was a significant association for neuroticism (R^2= 1.3%, p= **3.8E-03**) in this dataset, but none for agreeableness or conscientiousness. Of other outcomes, the association between depression (R^2= 2%, p= 3.8E-03), and loneliness (R^2= .9%, p= 5.3E-02) and subjective wellbeing (R^2= 3.1%; p= 3.1E-04) were also

significant in CogBIAS. However, there were no significant associations between ADHD, anxiety, autism, insomnia or educational attainment.

The CogBIAS data included more SNPs than TEDS, but it had a smaller sample size, which may explain why some of the findings were not repeated across datasets. The replications across datasets for significant associations between sensitivity and PGS of openness, extraversion, subjective wellbeing, depression and loneliness provide strong support for these findings. PRSice authors recommend a significance threshold of p= .001 for the PGS, based on their permutation analyses. According to this significance threshold correction, the more robust associations in TEDS were for openness (p= 4.8E-05) and autism (p= 9.6E-04) and marginally extraversion (p= 4.9E-03), and in CogBIAS they were extraversion (p= 3.4E-04), subjective wellbeing (p= 3.1E-04) and marginally openness (p= 6.8E-03) and depression (p= 3.8E-03). The direction of effect (Beta-coefficients) for these significant associations were similar across data sets, such that PGS of openness, depression and autism were positively associated with sensitivity and PGS of extraversion and subjective wellbeing were negatively associated with sensitivity.

The results of the polygenic score analysis using the summary statistics from the meta-analysed TEDS and CogBIAS data largely reflected results in individual datasets. As expected, there were significant genetic correlations between sensitivity and openness (r^2= .02, p= 2.5E-06), extraversion (r^2 = .01, p= 1.9E-04), depression (r^2= .01, p= 3.5E-04), and autism (r^2= .01, p= 1.0E-04). Other traits with significant (p< .05) but smaller correlations included subjective wellbeing (r^2 = .006, p= 6.1E-03), neuroticism (r^2 = .005, p= 2.0E-02), ADHD (r^2 = .008, p= 2.6E-03), anxiety (r^2 = .006, p= 7.0E-03), and agreeableness (r^2= .005, p= 1.4E-02). No significant correlations were observed between sensitivity and conscientiousness, loneliness, insomnia, and educational attainment. The results of the cross-trait polygenic score analyses are summarised in **Table 4.13**. Bar-chart plots and high-resolution scoring graphs of TEDS, CogBIAS and meta-analysed data are presented in **Appendix 4.2**.

Overall, the results of cross-trait polygenic score analyses indicated PGS of neuroticism, anxiety, autism, openness, extraversion, and depression to be associated with sensitivity, with all six traits showing consistent direction of effect across the two datasets, and the latter four being robust to significance threshold correction of p< .001.

Table 4.13 Results of cross trait polygenic score analyses

	TEDS					CogBIAS					Meta-analysed data		
P_T	N SNPs	β	*S.E*	R^2	*p*	N SNPs	β	*S.E*	R^2	*p*	N SNPs	r_g	*p*
AGREEABLENSS													
.001	291	4.45	7.60	5.2E-04	5.6E-01	294	-1.33	8.66	5.7E-05	8.8E-01	286	3.4E-05	4.3E-01
.01	2307	43.16	24.95	4.5E-03	8.4E-02	2325	1.22	30.27	3.9E-06	9.7E-01	2227	9.2E-04	1.6E-01
.05	9070	33.75	57.56	5.2E-04	5.6E-01	9117	28.42	72.46	3.7E-04	7.0E-01	8208	5.8E-05	4.0E-01
.1	15770	14.5	83.04	4.6E-05	8.6E-01	15892	-19.12	97.84	9.2E-05	8.5E-01	13804	1.7E-04	3.4E-01
.2	26806	40.53	118.56	1.8E-04	7.3E-01	26995	13.13	146.05	2.0E-05	9.3E-01	22160	3.9E-05	4.2E-01
.3	35605	55	145.82	2.1E-04	7.1E-01	35934	-1.42	181.92	1.5E-07	9.9E-01	28518	1.0E-04	3.7E-01
.4	43313	44.21	170.26	1.0E-04	8.0E-01	43637	-41.23	212.28	9.1E-05	8.5E-01	33886	2.2E-04	3.2E-01
.5	49621	50.9	192.02	1.1E-04	7.9E-01	50036	-119.22	237.08	6.1E-04	6.2E-01	38154	3.5E-05	4.3E-01
1	68307	96.74	260.52	2.1E-04	7.1E-01	68766	-262.85	318.92	1.6E-03	4.1E-01	38157	3.5E-05	4.2E-01
Best	**1879**	**56.96**	**22.41**	**9.6E-03**	**1.1E-02**	20	2.87	2.14	4.3E-03	1.8E-01	**1827**	**4.7E-03**	**1.4E-02**
OPENNESS													
.001	289	9.66	6.75	3.1E-03	1.5E-01	289	2.01	7.38	1.8E-04	7.9E-01	294	1.3E-03	1.2E-01
.01	**2422**	**75.71**	**23.3**	**1.6E-02**	**1.2E-03***	2433	38.3	26.12	5.2E-03	1.4E-01	**2337**	**1.1E-02**	**3.2E-04***
.05	**9123**	**157.55**	**48.63**	**1.6E-02**	**1.3E-03***	9215	68.21	56.38	3.5E-03	2.3E-01	**8276**	**1.2E-02**	**1.6E-04***
.1	**15926**	**198.44**	**70.83**	**1.2E-02**	**5.2E-03**	16041	128.85	79.72	6.3E-03	1.1E-01	**13894**	**9.7E-03**	**7.5E-04***
.2	**26904**	**211.14**	**103.44**	**6.2E-03**	**4.2E-02**	27103	181.46	118.41	5.6E-03	1.3E-01	**22211**	**8.9E-03**	**1.2E-03***
.3	**35832**	**284.25**	**129.83**	**7.2E-03**	**2.9E-02**	36044	265.82	151.61	7.4E-03	8.0E-02	**28681**	**1.1E-02**	**3.3E-04***
.4	**43224**	**322.84**	**149.72**	**7.0E-03**	**3.1E-02**	43513	269.44	176.06	5.6E-03	1.3E-01	**33868**	**1.2E-02**	**2.0E-04***
.5	**49466**	**379.61**	**168.28**	**7.6E-03**	**2.4E-02**	49871	267.87	199.5	4.3E-03	1.8E-01	**38141**	**1.2E-02**	**1.8E-04***
1	**68182**	**491.31**	**227.37**	**7.0E-03**	**3.1E-02**	68680	375.34	267.38	4.7E-03	1.6E-01	**38146**	**1.2E-02**	**1.7E-04***
Best	**1385**	**68.08**	**16.62**	**2.5E-02**	**4.8E-05***	**3039**	**79.28**	**29.11**	**1.8E-02**	**6.8E-03**	**5677**	**2.0E-02**	**2.5E-06***

Table 4.13 Continued

	TEDS					CogBIAS					Meta-analysed data		
P_T	N SNPs	β	*S.E*	R^2	*p*	N SNPs	β	*S.E*	R^2	*p*	N SNPs	r_g	*p*
CONSCIENTIOUSNESS													
.001	322	9.79	6.81	3.1E-03	1.5E-01	324	-9.9	7.61	4.1E-03	1.9E-01	317	9.1E-04	1.7E-01
.01	2370	31.61	20.75	3.5E-03	1.3E-01	2388	-8.00	23.94	2.7E-04	7.4E-01	2259	4.0E-04	2.6E-01
.05	9147	43.67	47.06	1.3E-03	3.5E-01	9240	-23.33	54.32	4.4E-04	6.7E-01	8255	3.5E-04	2.7E-01
.1	15951	106.1	66.25	3.8E-03	1.1E-01	16068	-50.65	76.83	1.0E-03	5.1E-01	13834	3.0E-04	2.9E-01
.2	26953	166.79	93.23	4.8E-03	7.4E-02	27186	-62.5	112.72	7.4E-04	5.8E-01	22325	4.1E-04	2.6E-01
.3	35779	215.93	116.78	5.1E-03	6.5E-02	36085	-89.49	144.08	9.3E-04	5.3E-01	28650	3.6E-05	4.2E-01
.4	43155	200.42	138.25	3.2E-03	1.5E-01	43560	-79.76	168.3	5.4E-04	6.4E-01	33758	2.6E-06	4.8E-01
.5	49671	179.59	155.75	2.0E-03	2.5E-01	50084	-123.81	191.57	1.0E-03	5.2E-01	38219	1.0E-04	3.7E-01
1	68239	178.22	211.14	1.1E-03	4.0E-01	68713	-134.63	256.58	6.6E-04	6.0E-01	38222	1.0E-04	3.7E-01
Best	**167**	**10.08**	**4.68**	**6.9E-03**	**3.2E-02**	313	-12.26	7.48	6.4E-03	1.0E-01	17430	1.7E-03	9.5E-02
NEUROTICISM													
.001	956	-31.43	201.7	3.7E-05	8.8E-01	960	340.48	221.07	5.7E-03	1.2E-01	905	2.3E-03	6.1E-02
.01	4332	255.54	546.05	3.3E-04	6.4E-01	**4388**	**1291.52**	**620.62**	**1.0E-02**	**3.8E-02**	3931	1.1E-03	1.4E-01
.05	12838	1658.14	1081.67	3.5E-03	1.3E-01	13000	2040.5	1290.47	6.0E-03	1.1E-01	**11220**	**2.9E-03**	**4.1E-02**
.1	20241	1966.06	1482.86	2.6E-03	1.9E-01	20534	3220.32	1765.06	8.0E-03	6.9E-02	**17159**	**3.3E-03**	**3.1E-02**
.2	31943	3078	2093.81	3.2E-03	1.4E-01	32399	3845.88	2473.14	5.8E-03	1.2E-01	**25871**	**4.3E-03**	**1.7E-02**
.3	41236	3133.94	2593.82	2.2E-03	2.3E-01	41720	4923.66	3007.83	6.4E-03	1.0E-01	**32555**	**3.3E-03**	**3.1E-02**
.4	48728	4252.09	2970.35	3.1E-03	1.5E-01	49341	6207.78	3515.77	7.5E-03	7.8E-02	**37747**	**3.7E-03**	**2.5E-02**
.5	55088	4247.84	3302.53	2.5E-03	2.0E-01	55735	6772.72	3894.59	7.2E-03	8.3E-02	42071	2.4E-03	5.6E-02
1	72652	4824.11	4319.7	1.9E-03	2.6E-01	73518	8393.87	5035.22	6.7E-03	9.6E-02	42075	2.4E-03	5.6E-02
Best	15317	2138.62	1214.50	4.6E-03	7.9E-02	**5318**	**1627.29**	**694.74**	**1.3E-02**	**2.0E-02**	**25104**	**5.1E-03**	**1.1E-02**

Table 4.13 Continued

	TEDS					CogBIAS					Meta-analysed data		
P_T	N SNPs	β	*S.E*	R^2	*p*	N SNPs	β	*S.E*	R^2	*p*	N SNPs	r_g	*p*
EXTRAVERSION													
.001	84	-49.06	45.96	1.7E-03	2.9E-01	84	-36.05	54.22	1.1E-03	5.1E-01	88	1.7E-03	9.2E-02
.01	573	-48.98	136.66	1.9E-04	7.2E-01	576	-277.6	160.78	7.1E-03	8.5E-02	**540**	**2.8E-03**	**4.4E-02**
.05	2043	-327.25	294.14	1.9E-03	2.7E-01	**2059**	**-1020.51**	**336.93**	**2.2E-02**	**2.6E-03**	**1846**	**7.3E-03**	**3.0E-03**
.1	3412	-407.87	408.66	1.5E-03	3.2E-01	**3461**	**-1103.37**	**474.43**	**1.3E-02**	**2.1E-02**	**2917**	**1.0E-02**	**5.2E-04***
.2	5600	-530.95	566.22	1.3E-03	3.5E-01	**5687**	**-1475.78**	**682.78**	**1.1E-02**	**3.1E-02**	**4562**	**9.5E-03**	**8.6E-04***
.3	7179	-810.73	672.61	2.2E-03	2.3E-01	**7311**	**-1916.98**	**840.74**	**1.2E-02**	**2.3E-02**	**5673**	**1.1E-02**	**3.5E-04***
.4	8565	-1028.84	771.65	2.7E-03	1.8E-01	**8690**	**-2090**	**980.95**	**1.1E-02**	**3.4E-02**	**6619**	**1.2E-02**	**2.3E-04***
.5	9638	-1128.21	851.2	2.6E-03	1.9E-01	**9787**	**-2121.41**	**1086.96**	**9.1E-03**	**5.2E-02**	**7344**	**1.0E-02**	**5.2E-04***
1	12582	-1599.89	1097.82	3.2E-03	1.5E-01	12715	-2583.02	1410.67	8.0E-03	6.8E-02	**7344**	**1.0E-02**	**5.2E-04***
Best	**3**	**-20.40**	**7.22**	**1.2E-02**	**4.9E-03**	**2803**	**-1449.77**	**400.79**	**3.1E-02**	**3.4E-04***	**1283**	**1.2E-02**	**1.9E-04***
ADHD													
.001	879	99.64	57.43	4.5E-03	8.3E-02	887	53.77	63.27	1.7E-03	4.0E-01	**817**	**2.6E-03**	**5.2E-02**
.01	**3979**	**274.45**	**143.72**	**5.5E-03**	**5.7E-02**	4001	176.87	173.18	2.5E-03	3.1E-01	**3634**	**5.8E-03**	**7.0E-03**
.05	11866	493.17	280.53	4.6E-03	7.9E-02	11977	190.07	333.38	7.8E-04	5.7E-01	**10294**	**3.8E-03**	**2.4E-02**
.1	18922	583.25	386.51	3.4E-03	1.3E-01	19159	-34.67	470.9	1.3E-05	9.4E-01	**15936**	**2.5E-03**	**5.5E-02**
.2	29737	189.55	533.71	1.9E-04	7.2E-01	30105	-20.72	633.9	2.6E-06	9.7E-01	24093	1.1E-03	1.4E-01
.3	38390	214.87	646.46	1.7E-04	7.4E-01	38809	-345.3	780.56	4.7E-04	6.6E-01	30417	7.5E-04	1.9E-01
.4	45447	251.83	748.86	1.7E-04	7.4E-01	45997	-478.06	900.56	6.8E-04	6.0E-01	35365	1.1E-03	1.4E-01
.5	51562	251.14	831.96	1.4E-04	7.6E-01	52199	-529.51	999.7	6.8E-04	6.0E-01	39552	9.9E-04	1.6E-01
1	69121	366.42	1093.13	1.7E-04	7.4E-01	70006	-695.19	1335.48	6.5E-04	6.0E-01	39555	9.9E-04	1.6E-01
Best	**4510**	**343.98**	**156.10**	**7.3E-03**	**2.8E-02**	1071	106.21	73.30	5.0E-03	1.5E-01	**2619**	**7.5E-03**	**2.6E-03**

Table 4.13 Continued

	TEDS					CogBIAS					Meta-analysed data		
P_T	N SNPs	β	*S.E*	R^2	*p*	N SNPs	β	*S.E*	R^2	*p*	N SNPs	r_g	*p*
ANXIETY													
.001	434	121.4	91.92	2.6E-03	1.9E-01	432	-2.37	105.64	1.2E-06	9.8E-01	**425**	**2.8E-03**	**4.5E-02**
.01	3257	253.26	281.95	1.2E-03	3.7E-01	3274	-22.95	342.65	1.1E-05	9.5E-01	**3101**	**4.7E-04**	**2.4E-01**
.05	12074	531.04	652.63	1.0E-03	4.2E-01	12157	768.11	774.25	2.4E-03	3.2E-01	**10789**	**2.2E-03**	**6.5E-02**
.1	20541	1106.29	907.03	2.2E-03	2.2E-01	20786	1492.73	1095.78	4.5E-03	1.7E-01	**17574**	**3.8E-03**	**2.4E-02**
.2	32970	1975.52	1280.99	3.6E-03	1.2E-01	33321	2288.71	1570.54	5.1E-03	1.5E-01	**26832**	**4.0E-03**	**2.0E-02**
.3	42579	1295.83	1566.84	1.0E-03	4.1E-01	43035	2109.24	1917.27	2.9E-03	2.7E-01	33484	2.3E-03	6.1E-02
.4	50063	1193.69	1785.84	6.7E-04	5.0E-01	50647	2391.45	2195.88	2.9E-03	2.8E-01	38577	1.4E-03	1.1E-01
.5	55923	1372.43	1955.35	7.4E-04	4.8E-01	56561	2557.18	2411.99	2.7E-03	2.9E-01	42569	2.1E-03	7.0E-02
1	71483	1309.49	2475.47	4.2E-04	6.0E-01	72214	3275.99	3025.07	2.8E-03	2.8E-01	42575	2.1E-03	7.0E-02
Best	**981**	**353.78**	**146.48**	**8.7E-03**	**1.6E-02**	16426	1692.07	945.09	7.7E-03	7.4E-02	**16198**	**5.8E-03**	**7.0E-03**
AUTISM													
.001	395	36.86	22.42	4.1E-03	1.0E-01	398	41.23	26.68	5.7E-03	1.2E-01	**378**	**5.9E-03**	**6.8E-03**
.01	**2773**	**136.96**	**71.64**	**5.5E-03**	**5.6E-02**	2783	66.02	83.32	1.5E-03	4.3E-01	**2598**	**3.9E-03**	**2.3E-02**
.05	10074	30.19	151.55	6.0E-05	8.4E-01	10190	0.28	172.98	6.3E-09	1.0E+00	9018	2.9E-04	2.9E-01
.1	17191	-29.85	208.02	3.1E-05	8.9E-01	17372	-106.92	249.68	4.4E-04	6.7E-01	14759	4.8E-05	4.1E-01
.2	28585	-194.34	293.13	6.6E-04	5.1E-01	28883	101.97	346.72	2.1E-04	7.7E-01	23303	1.6E-05	4.5E-01
.3	37623	-211.5	366.47	5.0E-04	5.6E-01	38007	244.21	423.12	8.0E-04	5.6E-01	29782	5.5E-05	4.1E-01
.4	45234	-310.28	422.83	8.1E-04	4.6E-01	45722	410.36	486.55	1.7E-03	4.0E-01	35086	9.1E-07	4.9E-01
.5	51702	-261.18	476.03	4.5E-04	5.8E-01	52345	457.64	544.98	1.7E-03	4.0E-01	39506	5.9E-05	4.0E-01
1	70503	-318.23	639.74	3.7E-04	6.2E-01	71325	670.74	733.77	2.0E-03	3.6E-01	39512	5.5E-05	4.1E-01
Best	**127**	**40.07**	**12.08**	**1.6E-02**	**9.6E-04***	177	31.25	16.95	8.0E-03	7.0E-02	**252**	**1.0E-02**	**1.0E-04***

Table 4.13 Continued

DEPRESSION													
.001	641	266.18	183.74	3.2E-03	1.5E-01	646	11.94	220.33	7.1E-06	9.6E-01	620	5.1E-04	2.3E-01
.01	3884	339.05	552.12	5.7E-04	5.4E-01	**3915**	**1493.38**	**639.03**	**1.3E-02**	**2.0E-02**	**3631**	**4.8E-03**	**1.2E-02**
.05	12486	1460.84	1189.33	2.3E-03	2.2E-01	**12614**	**3302.37**	**1314.97**	**1.5E-02**	**1.2E-02**	**10954**	**8.0E-03**	**1.9E-03***
.1	20386	369.11	1640.58	7.6E-05	8.2E-01	**20546**	**3786.15**	**1845.69**	**1.0E-02**	**4.1E-02**	**17239**	**3.1E-03**	**3.7E-02**
.2	32442	813.68	2236.18	2.0E-04	7.2E-01	**32812**	**5840.58**	**2533.47**	**1.3E-02**	**2.2E-02**	**26191**	**3.0E-03**	**3.9E-02**
.3	41728	1773.57	2730.77	6.3E-04	5.2E-01	**42222**	**7569.68**	**3060.73**	**1.5E-02**	**1.4E-02**	**32859**	**3.4E-03**	**3.1E-02**
.4	49355	1065.6	3142.65	1.7E-04	7.3E-01	**49859**	**7774.75**	**3496.18**	**1.2E-02**	**2.7E-02**	**38098**	**3.5E-03**	**2.9E-02**
.5	55660	1445.53	3484.21	2.6E-04	6.8E-01	**56149**	**8646.01**	**3898.56**	**1.2E-02**	**2.7E-02**	**42242**	**3.6E-03**	**2.7E-02**
1	72440	363	4467.8	9.9E-06	9.4E-01	**73295**	**11196.08**	**5085.5**	**1.2E-02**	**2.8E-02**	**42248**	**3.6E-03**	**2.7E-02**
Best	**7986**	**1782.61**	**876.33**	**6.2E-03**	**4.2E-02**	**16231**	**4586.44**	**1574.04**	**2.0E-02**	**3.8E-03**	**9887**	**1.1E-02**	**3.5E-04***
EDUCATIONAL ATTAINMENT													
.001	1908	190.16	389.9	3.6E-04	6.3E-01	1925	-345.11	453.96	1.4E-03	4.5E-01	1691	3.2E-04	2.8E-01
.01	5999	1449.79	816.48	4.7E-03	7.6E-02	6079	-561.21	988.85	7.8E-04	5.7E-01	5269	7.3E-04	1.9E-01
.05	14813	2295.55	1491.04	3.6E-03	1.2E-01	14998	29.52	1741.88	6.9E-07	9.9E-01	12525	4.0E-04	2.6E-01
.1	22192	2457.79	1972.38	2.3E-03	2.1E-01	22488	-765.85	2288.18	2.7E-04	7.4E-01	18271	4.7E-05	4.1E-01
.2	33349	2783.27	2603.99	1.7E-03	2.9E-01	33747	-1856.03	3064.26	8.8E-04	5.5E-01	26632	1.1E-04	3.7E-01
.3	42183	3448.7	3165.53	1.8E-03	2.8E-01	42647	-2093	3651.28	7.9E-04	5.7E-01	32802	2.5E-04	3.1E-01
.4	49541	4234.88	3634.36	2.0E-03	2.4E-01	50043	-2060.68	4192.63	5.8E-04	6.2E-01	37930	3.7E-04	2.7E-01
.5	55741	4897.39	4046.98	2.2E-03	2.3E-01	56262	-2113.64	4598.5	5.1E-04	6.5E-01	42223	1.9E-04	3.3E-01
1	73586	5578.98	5241.43	1.7E-03	2.9E-01	74239	-3135.83	5997.58	6.6E-04	6.0E-01	42229	1.8E-04	3.3E-01
Best	**8694**	**2247.35**	**1046.20**	**6.9E-03**	**3.2E-02**	2519	-667.56	546.24	3.6E-03	2.2E-01	5698	1.9E-03	7.9E-02

Table 4.13 Continued

INSOMNIA													
.001	513	-59.68	70.87	1.1E-03	4.0E-01	512	-10.94	78.2	4.7E-05	8.9E-01	492	2.6E-04	3.0E-01
.01	3151	-81.00	197.04	2.5E-04	6.8E-01	3179	145.32	229.56	9.7E-04	5.3E-01	2965	3.3E-05	4.3E-01
.05	10780	187.15	415.64	3.1E-04	6.5E-01	10917	318.44	529.46	8.7E-04	5.5E-01	9609	4.0E-04	2.6E-01
.1	18209	-41.91	588.82	7.6E-06	9.4E-01	18442	423.12	733.19	8.0E-04	5.6E-01	15632	8.8E-05	3.8E-01
.2	29744	196.10	800.29	9.0E-05	8.1E-01	30066	126.79	1001.35	3.9E-05	9.0E-01	24419	5.3E-05	4.1E-01
.3	39180	7.16	992.37	7.8E-08	9.9E-01	39574	-108.17	1234.9	1.9E-05	9.3E-01	31164	2.6E-05	4.3E-01
.4	47116	-28.58	1155.77	9.2E-07	9.8E-01	47572	-412.83	1436.76	2.0E-04	7.7E-01	36631	1.0E-05	4.6E-01
.5	53858	287.38	1286.38	7.5E-05	8.2E-01	54387	-381.29	1615.22	1.3E-04	8.1E-01	41306	6.0E-06	4.7E-01
1	73561	967.55	1740.26	4.7E-04	5.8E-01	74257	-333.67	2178.15	5.7E-05	8.8E-01	41306	6.0E-06	4.7E-01
Best	871	-134.67	92.38	3.2E-03	1.5E-01	4993	307.56	302.00	2.5E-03	3.1E-01	1667	2.1E-03	7.2E-02
LONELINESS													
.001	287	-4.26	18.68	7.8E-05	8.2E-01	287	32.2	22.48	4.9E-03	1.5E-01	285	1.6E-04	3.4E-01
.01	2217	-67.07	63.49	1.7E-03	2.9E-01	2234	119.88	73.14	6.4E-03	1.0E-01	2136	1.8E-05	4.5E-01
.05	8499	-196.61	141.84	2.9E-03	1.7E-01	8614	236.84	168.42	4.7E-03	1.6E-01	7732	3.8E-05	4.2E-01
.1	**15034**	**-422.9**	**205.96**	**6.3E-03**	**4.0E-02**	15200	251.73	241.53	2.6E-03	3.0E-01	13165	6.9E-06	4.7E-01
.2	25754	-508.62	303.23	4.2E-03	9.4E-02	26128	401.9	354.28	3.1E-03	2.6E-01	21488	1.1E-04	3.7E-01
.3	34395	-697.01	379.36	5.1E-03	6.7E-02	34949	396.99	447.49	1.9E-03	3.8E-01	27921	8.9E-06	4.6E-01
.4	41805	-711.61	438.51	4.0E-03	1.1E-01	42427	465.96	516.5	2.0E-03	3.7E-01	33160	1.6E-05	4.5E-01
.5	48052	-639.73	495.18	2.5E-03	2.0E-01	48753	502.07	583.75	1.8E-03	3.9E-01	37422	3.2E-05	4.3E-01
1	66669	-821.71	682.87	2.2E-03	2.3E-01	67393	701.88	795.43	1.9E-03	3.8E-01	37422	3.2E-05	4.3E-01
Best	**14725**	**-443.64**	**204.34**	**7.0E-03**	**3.0E-02**	**6029**	**262.73**	**135.62**	**9.0E-03**	**5.3E-02**	5902	1.1E-03	1.4E-01

Table 4.13 Continued

	TEDS					CogBIAS					Meta-analysed data		
P_T	N SNPs	β	*S.E*	R^2	*p*	N SNPs	β	*S.E*	R^2	*p*	N SNPs	r_g	*p*
SUBJECTIVE WELLBEING													
.001	541	-159.5	136.88	2.0E-03	2.4E-01	542	-248.17	167.46	5.3E-03	1.4E-01	**299**	**2.7E-03**	**4.7E-02**
.01	3233	-179.91	421.99	2.7E-04	6.7E-01	**3250**	**-1712.57**	**491.8**	**2.8E-02**	**5.5E-04***	1757	1.6E-03	9.9E-02
.05	10620	-586.05	878.98	6.7E-04	5.1E-01	**10729**	**-2887.42**	**1040.16**	**1.8E-02**	**5.8E-03**	5259	1.1E-03	1.5E-01
.1	17798	107.88	1273.01	1.1E-05	9.3E-01	**17876**	**-3668.68**	**1447.26**	**1.5E-02**	**1.2E-02**	8571	3.8E-05	4.2E-01
.2	28906	483.27	1806.91	1.1E-04	7.9E-01	**29064**	**-4777.27**	**2091.03**	**1.2E-02**	**2.3E-02**	13395	1.3E-05	4.5E-01
.3	37662	-172.12	2215.84	9.1E-06	9.4E-01	**37991**	**-5328.51**	**2565.9**	**1.0E-02**	**3.8E-02**	17013	5.1E-06	4.7E-01
.4	44887	-143.19	2584.25	4.6E-06	9.6E-01	**45170**	**-6410.16**	**2925.87**	**1.1E-02**	**2.9E-02**	19898	1.5E-05	4.5E-01
.5	51050	-743.67	2927.59	9.7E-05	8.0E-01	**51494**	**-6527.08**	**3286.65**	**9.4E-03**	**4.8E-02**	22289	7.9E-06	4.6E-01
1	68952	-756.08	3875.3	5.7E-05	8.5E-01	**69446**	**-8742.02**	**4393.82**	**9.5E-03**	**4.7E-02**	22295	5.6E-06	4.7E-01
Best	**98**	**-123.40**	**50.76**	**8.8E-03**	**1.5E-02**	**6630**	**-2833.26**	**778.17**	**3.1E-02**	**3.1E-04***	**434**	**6.1E-03**	**6.1E-03**

P_T= *P*-value threshold for inclusion of SNPs in the model; Best= PGS at best threshold (highest Beta and lowest *p*); $p < .05$ are in bold; * *p*-value significant after multiple testing correction at $p < .001$

4.4 Discussion

The aims of this chapter were to examine the molecular genetic factors underlying the detected heritability of environmental sensitivity. Two distinct methodological approaches were applied to do this. First, a hypothesis-driven approach was taken by examining whether any of the previous genetic variants, found to moderate the effects of environmental influences consistent with differential susceptibility theories, may explain individual differences in environmental sensitivity. The associations between these genetic variants and sensitivity were examined at a variant and a gene level. Second, a hypothesis-free approach was taken by examining the genome-wide associations between environmental sensitivity and over 3 million common SNPs, as well as over 18,000 genes and 10,000 gene-systems that are believed to have functional consequences for biological pathways involved in human development. The genome-wide approaches included GWAS, gene-based, gene-set as well as polygenic score analysis. Within these two distinct approaches, an important consideration was given to replicability, therefore the analyses were conducted across multiple datasets and the results were meta-analysed. A discussion of findings from these analyses are presented in the sections below, separately for candidate gene and genome-wide approaches, followed by evaluation of the limitations and implications of the studies herein, directions for future studies, and a final conclusion

4.4.1 Candidate gene analysis findings

In the candidate gene analysis, the main hypothesis was that the genetic variants that have been found to moderate the impact of environmental influences for better and for worse in previous differential susceptibility GxE studies, would be associated with individual differences in environmental sensitivity, as measured via a validated questionnaire in adolescents. The effects of variation in five VNTRs (*5-HTTLPR, DRD4, MAOA, DAT1, STin2*) were analysed, each having shown prior evidence of moderating the effects of a range of environmental factors in a manner consistent with differential susceptibility theories. In addition to this, the associations between environmental sensitivity and candidate sensitivity genes was examined using a gene-based model, with the unit of association being the summarised gene-values rather than single SNPs within it. The analysis using VNTRs were examined in STRATEGIES data only, as they were not available in other datasets. The results from the VNTR analyses did not yield any significant associations between the five studied variants and environmental sensitivity. The direction of associations for *DAT1*, *DRD4* and *STin2*

VNTRs were not in the expected direction either, where higher number of sensitivity alleles in these VNTRs associated with lower levels of environmental sensitivity.

For gene-based analysis, associations were examined in three datasets (STRATEGIES (*N*= 838), TEDS (*N*=642) and CogBIAS (*N*= 295)). The results from gene-based analysis of 19 candidate genes identified significant associations for three genes: *HTR2A*, *ESR1*, and *COMT* in TEDS data. None of the significant associations were replicated across the other two datasets, and the associations were not robust to multiple testing correction. *HTR2A* gene encodes one of the receptors for serotonin (*5-HT2* receptors), which are primarily located in neocortex, caudate nucleus, nucleus accumbens, hippocampus, and smooth muscle cells. *ESR1* encodes an estrogen receptor, which play an important role in hormone binding, DNA binding, and activation of transcription. Estrogen and its receptors are essential for sexual development and reproductive function, as well as pathological processes including breast cancer, endometrial cancer, and osteoporosis. *COMT* gene encodes the catechol-*O*-methyltransferase protein, which is involved in the degradation of catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine. *COMT* is one of the genes with the strongest evidence of their differential susceptibility effect on environmental factors. Variations in *COMT* VNTR for example, has been found to moderate the effects of prenatal smoking and aggressive behaviour in adolescents (Brennan et al., 2011), parenting quality on alcohol use (Laucht et al., 2012), childhood trauma on anxiety sensitivity (Baumann et al., 2013), and serious life events on childhood aggression (Hygen et al., 2015). Though examined in smaller number of studies, *HTR2A,* and *ESR1* have been nominated as sensitivity candidate genes for moderating the influence of childhood maternal nurturance on adult social attachment (Salo et al., 2011), and familial conflict/cohesion and onset of menarche (Manuck et al., 2011).

Despite these genes having been found to be associated with environmental sensitivity in the current study, the significant associations were found only in one sample out of the three, and none remained significant following correction for multiple testing. The significant results must therefore be interpreted very cautiously. Lack of significant associations between the phenotype of environmental sensitivity and some of the most robust sensitivity candidate VNTRs such as *5-HTTLPR, MAOA* and *COMT,* may be interpreted from two angles: a) the current null findings hold true and that these variants are not implicated or as relevant to environmental sensitivity, despite strong evidence

from previous studies, b) the null findings represent a type II error, where there is an effect, but the current study failed to detect it, due to the limitations discussed later on in this section.

The first interpretation is plausible in light of two main points. First, previous GxE studies and the current study differ in how they conceptualised environmental sensitivity. That is, GxE studies capture operational sensitivity as variations in a measured response (e.g. depression/no depression) to a specific measured environmental influence (e.g. traumatic life events), whereas the current study measures sensitivity as a personality trait, hypothesised to be relatively stable across time and context of an individual. This latter conceptualisation means that while the overall pattern of behaviour may reflect generally heightened sensitivity to environmental stimuli, the reactions/outcomes in specific context may not consistently reflect this. The opposite holds for the operational concept of sensitivity in GxE studies, where responses are context/outcome specific. This is more evident when we have a closer look at the range of environmental factors and outcomes that are generally studied with each candidate gene. For example, *SLC6A4* and other serotonin system genes are commonly studied in the context of stressful/traumatic life events and internalising behaviours, whereas *DRD4* is commonly studied with externalising behaviours, mainly due to these genes hypothesised biological relevance for these psychological outcomes, rather than because they are specifically related to the phenotype of environmental sensitivity. As noted in the introduction, the same genes that underlie significant differential response to environmental influences may therefore not be implicated as strongly in the phenotype of sensitivity. This interpretation is also supported by Chen et al. (2011), who showed that several of the dopaminergic candidate sensitivity genes (*DRD4*, *DAT1, COMT* and *MAOA*) selected from previous GxE studies were not significantly associated with variations in the environmental sensitivity phenotype.

The second point that further validates the possibility the candidate gene findings are truly null, relates to the fundamental limitation of candidate gene approaches. That is, the methodological issues such as vague biological hypothesis for candidate gene selection, and most importantly, that the effect of single or multiple gene variants on complex traits is so small that the significant findings from previous GxE studies most likely reflect false positives, in these largely underpowered samples. Though it is true that the samples used in the current study were also underpowered to detect the more realistic effect sizes (< .02%) for these variants, it was sufficiently powered to detect the

kind of effects reported in previous candidate GxE studies. For example, Pluess et al. (2010) found a significant interaction effect consistent with differential susceptibility for *5-HTTLPR* and life events in predicting neuroticism, in a sample of 118 individuals. The effect size for the interaction was $f^2 = .04$. Considering that interactions are statistically harder to detect than main effects (Duncan & Keller, 2011; Munafo & Flint, 2009), and the STRATEGIES sample was almost 8 times larger and better powered to find a similar effect size, but failed to do so, further strengthen the proposition that the candidate genes identified through GxE studies may not be as robust as they appear. In light of these limitations, it is possible that none of the previously hypothesised sensitivity genes can be considered robust candidates that play a large or significant role in the biological aetiology of a complex trait such as the phenotype of environmental sensitivity. If sufficiently powered studies that search the entire genome for associations find only tiny effects, then large effects found in studies with sample sizes in hundreds are likely to be false positives. This has been shown empirically for general intelligence (g) for example, where using a sample of 10,000 participants, Chabris et al. (2012) failed to replicate the associations between g and 12 candidate genes.

The second interpretation, that the null results from the current study represent a type II error, may be plausible in light of the methodological differences in the current study versus previous candidate gene studies. For example, while previous studies used a purely hypothesis-driven approach, by examining a specific SNP within a gene and specifying which allele in each SNP is the sensitivity allele, the gene-based method included all SNPs within a gene and did not specify the sensitivity allele for the included SNPs in a gene. Another point related to this, is how rare alleles are treated across different studies of VNTRs. While some exclude these individuals, other studies assimilate them into the main genotype categories (e.g. 5 or 6 repeats are grouped with more prevalent 7 repeats), yet others create a separate genotype category (e.g. 7R, 9R, other). Since there is no clear consensus across studies, the approach depends on the sample characteristics and the authors' choice. The approach in the current study was to exclude those individuals with rare alleles, however, the difference in the approach taken here versus other studies is unlikely to be an important influencer since the number of excluded individuals were small. The other potential reason for this study not finding significant associations for candidate genes may be due to the measure of the phenotype of sensitivity. It is possible that the sensitivity reflected in the Highly Sensitive Personality scale reflects more negative aspect of sensitivity, which would bias the results towards associations that reflect negative sensitivity rather than

sensitivity to both positive and negative influences. This is plausible, considering the findings from **Chapter 2,** showing that sensitivity as captured by the HSC scale was more strongly associated with negative outcomes such as depression, anxiety and neuroticism. In addition, the heritability analyses in **Chapter 3** found that the three subscales of HSC capture the general domain of sensitivity, but also that its subscales reflect more specific aspects of sensitivity, such as sensitivity to more positive appraisal of environmental exposures through AES, sensitivity to more negative appraisal of environmental influences as through EOE, and heightened negative reactivity to unpleasant sensory sensations through LST. Examining the genetic associations of these relatively distinct components may have shown different associations with these candidate genes and sensitivity. Though important to consider, the subscales were not examined in the current chapter due to the scope of the thesis and the need for multiple testing correction for three additional sets of analyses, which would have gravely impacted the power.

Overall, the results of candidate gene studies emphasised the limitation of candidate gene-approaches in examining the genetic basis of environmental sensitivity and that the top variants from GxE studies may not be most relevant to individual differences in environmental sensitivity.

4.4.2 Genome-wide analysis findings

In the genome-wide approaches the main aim was to take an exploratory approach to identify SNPs, genes and biological pathways that are significantly associated with individual differences in environmental sensitivity. To do this, first a GWAS was conducted to examine the associations between over 3 million common SNPs and environmental sensitivity. Gene-based analysis was then conducted to examine the association between over 18,000 functional genes across the genome and environmental sensitivity, followed by examination of the association between over 10,000 gene-sets belonging to biological pathways involved in human development and functioning. Finally, polygenic score analyses were conducted to examine the collective contribution of common SNPs to individual differences in environmental sensitivity. Similar to the candidate gene approaches, all analyses were conducted across both TEDS and CogBIAS where possible, and then meta-analysed.

GWAS analyses, conducted separately in TEDS and CogBIAS, did not identify any SNPs that were associated with environmental sensitivity at genome-wide significance

threshold values. This was expected since the sample sizes were too underpowered to detect the expected small effects of single SNPs. The top SNP in each dataset, rs4918121 (TEDS) and rs6435333 (CogBIAS), were located in *SORCS3* and *KCNJ3* genes respectively. *SORCS3* shows high expression of transcription factors in brain and adrenal glands and Alzheimer disease, and *KCNJ3* gene is involved in regulating heartbeat. Though highly speculative, it may be that variations in these genes may reflect the hypothesised physiological variations underlying sensitivity. Despite the potential lead, it was not possible to replicate the findings across datasets, since the top SNP from CogBIAS was not available in TEDS, and the top SNP in CogBIAS was not found to be significant in TEDS. Meta-analysis of the GWAS from the two samples identified rs17121012, located in the *LOC101926964* gene, as the top SNP across samples. Though the specific function of this gene is as yet uncharacterized, genes in this family have been found to be involved in pancreatic function and a range of cancers, including Pancreatic Ductal Adenocarcinoma. The other two genes identified through meta-analysis included *DHX35,* involved in embryogenesis, cellular grown and division, and *NFE2L2,* involved in response to injury and inflammation and oxidative stress. Though the results of the GWAS were exploratory, and did not find genome-wide significant hits due to low power, the results on the strength of association between these genetic variants and environmental sensitivity were used in down-stream polygenic score analyses which had more power to detect cumulative genetic effects.

Gene-based analyses resulted in one genome-wide significant hit in TEDS for the *LBX1* gene. *LBX1* is a protein-coding gene, with its homeobox transcription factor being involved in spinal cord differentiation and somatosensory signal transduction (Xu et al., 2012). This is an interesting finding, because of the hypothesised heightened sensory sensitivity aspect of environmental sensitivity, as reflected in highly sensitive personality. Variations in these genes therefore appear to be functionally relevant to the sensory differences in this trait. However, despite identifying one genome-wide significant and biologically relevant gene for environmental sensitivity, the association was not replicated in the CogBIAS data, perhaps due to the smaller sample size of CogBIAS, and the differences in age group, with CogBIAS including children of 13 years and TEDS adolescents of 17 years. In the meta-analysis across the two datasets, *LBX1* was still the top gene, though not genome-wide significant, proving further confidence that of all the 18,000 genes examined, *LBX1* was the most significantly associated with environmental sensitivity.

Gene-set analyses also identified one genome-wide significant gene-set (PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY) in TEDS. The genes in this gene-set reflect the serine/threonine phosphatase pathway activity, which are assumed to be relevant for the regulation of many cellular mechanisms, including cell differentiation, protein synthesis, apoptosis (programmed cell death) and embryonic development (Shi, 2009). This significant association for this gene-set, however, was not replicated in CogBIAS and subsequently did not appear as the top gene-set in the meta-analysis. The top gene-set from the meta-analysis was MIKKELSEN_ES_ICP_WITH_H3K4ME3_AND_H3K27ME3, with genes in this gene-set proposed to be relevant to expression and regulation of embryonic stem cells. While this gene-set was significant in both datasets, the p-value did not pass genome-wide corrected threshold. The lack of replication of the genome-wide significant hit from TEDS may be attributed to the low power in CogBIAS and differences in sample characteristics.

Polygenic score analyses were conducted using two main approaches, first, to predict environmental sensitivity in CogBIAS, based on a PGS of sensitivity from TEDS and also from a PGS of differential susceptibility, and second, to conduct cross-trait analysis to predict environmental sensitivity in TEDS and CogBIAS data, using PGS of a range of other related phenotypes (i.e. the Big Five personality traits), psychopathologies (autism, anxiety, depression, ADHD, insomnia, loneliness), and positive outcomes (wellbeing, educational attainment). Genetic correlation analyses were also conducted on the meta-analysed TEDS-CogBIAS GWAS summary statistics and these traits.

According to the results, the polygenic score of environmental sensitivity from TEDS explained 1.1% of the variance in environmental sensitivity in CogBIAS. The amount of variance explained was small, which is not surprising considering the small sample sizes in both discovery and replication steps. The significant prediction provided evidence that the genetic factors underlying variations in environmental sensitivity reflect a polygenic effect on the trait. Were the samples larger, the analysis would have had more power to explain larger amount of variance. The lack of more robust associations may also reflect the sample characteristics as noted earlier, with individuals from the different samples being at different developmental stages during data collection. Specifically, the phenotypic manifestations of environmental sensitivity, or subjective awareness of participants' own tendencies and reactions may be less developed in childhood than in adolescents. In addition, the contribution of genetic

effects to sensitivity may be increasing with age, a phenomenon that has been well established for a number of different complex phenotypes such as intelligence (Trzaskowski, Yang, Visscher, & Plomin, 2014)

The results of the polygenic score of differential susceptibility by Keers et al. (2016) predicting environmental sensitivity in CogBIAS was not found to be significant. The lack of a significant association may be due to two main factors. Firstly, the samples were small in both discovery (*N*= 1,026) and target (*N*= 395) datasets, meaning they were underpowered. Secondly, the polygenic score was created based on MZ twins differences on emotional symptoms, so although the scores represent differential reactivity to environmental influences that are relevant for emotional problems, they are biased towards heightened sensitivity to negative, rather than both positive and negative environmental influences, as environmental sensitivity is conceptualised to be.

The cross-trait polygenic score analyses yielded several significant associations, some of which were replicated across datasets and also robust to multiple testing correction. In TEDS there were significant associations between environmental sensitivity and PGS of all examined phenotypes, except for neuroticism and insomnia. In CogBIAS, there were significant associations between environmental sensitivity and PGS of openness, extraversion, neuroticism, depression, loneliness, and subjective wellbeing. The replications across datasets for significant associations between environmental sensitivity and PGS of openness, extraversion, subjective wellbeing, depression and loneliness, strengthened the evidence for these findings. These associations were robust to multiple testing correction for openness, extraversion, subjective wellbeing, autism, and depression. PGS of openness, extraversion, subjective wellbeing were the most predictive, explaining over 3% of the variation in environmental sensitivity, followed by depression at 2% and autism at 1.6%.

Polygenic score analyses on the meta-analysed TEDs and COGBIAS sample, further validated these findings. There were significant genetic correlations between subjective wellbeing, neuroticism, anxiety, autism, openness, extraversion and depression, with the latter four being robust to multiple testing correction. The cross-trait polygenic findings are consistent with evidenced phenotypic associations in previous research. High sensitivity has been associated with higher autistic symptoms (Liss, Mailloux, & Erchull, 2008), higher neuroticism (Smolewska et al., 2006; Sobocko & Zelenski, 2015), and higher anxiety and depression (Bakker & Moulding, 2012; Liss et al., 2008), but lower levels of life satisfaction (Booth et al., 2015) and extraversion (Smolewska et

al., 2006; Sobocko & Zelenski, 2015) and higher openness (Smolewska et al., 2006). The results thus suggest that the phenotypic correlations are partially due to overlapping genetic influences.

Apart from the phenotypic correlations, multivariate twin results with personality traits, depression and anxiety in **Chapter 3** provided initial support for the presence of shared genetic factors between environmental sensitivity and extraversion, neuroticism, anxiety, and depression. The polygenic score results supported the twin model findings for all four phenotypes, with depression being the most robust. This is perhaps due partly to the variation in the quality of the phenotype measures in the discovery sample, as larger samples technically provide more power, but impact the phenotype quality due to the greater mix of composite samples and phenotype measures.

4.4.3 Implications

The results from the current chapter have several implications for our understanding of the genetic factors underlying environmental sensitivity.

First, genome-wide polygenic approaches were found to be more suitable to studying environmental sensitivity than candidate gene approaches. Despite evidence from previous candidate GxE studies, the current study failed to detect any significant genetic main effects on the phenotype of environmental sensitivity. This indicates that previous studies might have put undue emphasis on candidate gene findings and that the genetic structure of environmental sensitivity seems to be more complicated than the serotoninergic and dopaminergic related genes most frequently studied. Though the current study was sufficiently powered to detect the effect sizes previously reported for these candidate genes, these variants were not found to be significant contributors to the phenotype of environmental sensitivity. While lack of a significant contribution does not negate the possibility that they are involved, it does indicate that these genetic factors do not contribute as much as expected. Instead, the findings from genome-wide approaches, especially the cross-trait correlations explained more of the variance in environmental sensitivity. This, due to the larger sample size of the discovery sample and also the methodological approach of calculating additive effects, indicates that genome-wide polygenic approaches may be more appropriate for studying the genetic basis of environmental sensitivity. The null findings also highlight that it is important to examine genetics of environmental sensitivity as a phenotype since it cannot be assumed that the same genes that appear to moderate the impact of specific

environmental influences are the same as those that reflect general tendencies in sensitivity to environmental influences, as the trait conceptualisation of sensitivity suggests.

Second, findings from the current study provides further evidence that environmental sensitivity, like other measures of personality, is a complex trait influenced by many genetic variants of small effect. Such effects may not be detected in GWAS of environmental sensitivity, unless much larger sample sizes are used.

Third, the polygenic score of common SNPs explained a small proportion of variance in environmental sensitivity. As shown in **Chapter 3**, the heritability of environmental sensitivity was estimated at 47 %, using twin design. This is almost 15 times larger than the best polygenic score could predict at 3%. While, this "missing heritability" in molecular genetic studies (Maher, 2008) is partly a function of low power to detect smaller effects, other potential mechanisms have been proposed, including the contribution of other variants not included in polygenic scores such as CNVs, epigenetic processes, or GxE interactions. The results from the current study indicate the importance of using sufficiently powered samples, but also investigating the genetics of environmental sensitivity in the context of these other variations.

Fourth, cross-trait approaches are promising and can be informative in understanding the genetics of environmental sensitivity. The findings from cross-trait polygenic analyses confirmed the results of multivariate twin analysis from **Chapter 3**, showing that although environmental sensitivity and common personality traits have distinct phenotypic presentations, they share a substantial genetic basis. This was the first study to examine the genetic correlation between these traits using molecular genetic data. While genetics of environmental sensitivity is a new area of research, personality and other psychiatric outcomes have been studied for longer, with more developed biological hypotheses and correlates. In order to understand environmental sensitivity, we can build on the existing research on these better studied traits to examine how they relate to mechanism involved in environmental sensitivity, or those that leads to their phenotypic co-presentation and distinctiveness.

Fifth, genome-wide results indicated that genes and pathways other than those implicated in the brain may be relevant for individual differences in environmental sensitivity. The exploratory GWAS, gene-based and gene-set analyses identified several novel genes as candidate sensitivity genes and future research might benefit from

widening the search to genes beyond the dopamine and serotonin system genes, to those that are more broadly expressed and involved in embryonic development and other physiological systems not directly implicated in brain function.

4.4.4 Strengths and limitations

The main strengths of the current study were this being the largest candidate genes study of environmental sensitivity phenotype and the first ever genome-wide study of this trait. In addition, the most recent approaches in behavioural genetic research were applied to studying environmental sensitivity including gene-based and gene-set analysis to explore its genetics from a functional biological perspective. The use of multiple samples and meta-analysis allowed greater sensitivity and assessment of the reliability of significant findings. There were, however, several limitations. Firstly, all of the analyses conducted here were only able to capture main effects of genetic variation on environmental sensitivity. A more comprehensive investigation would have involved examining polygenic x E effects on individual differences in environmental sensitivity, which would enable identifying genes that are indirectly involved in this trait through their interaction with environmental influences. Secondly, the GWAS analyses were underpowered and exploratory, and the results should be considered preliminary only. While there was sufficient power to detect polygenic effects, the small sample size from the initial discovery in TEDS meant that the study were largely underpowered to predict sensitivity in CogBIAS or to detect smaller effects in cross-trait analyses. Thirdly, the analyses investigated only the total score from the highly sensitive personality scale. Despite the previous heritability analyses indicating that distinct genetic influences may underlie the three subscales of the measure, these were not examined separately for their molecular genetic associations. Conducting separate analysis on the subscales might have revealed genetic factors that are not captured by the total score. The decision to not pursue this line of analysis in the current chapter was made due to considerations for power and general scope of the thesis. Finally, the current study included children and adolescents, which may limit extending of the findings to adults. The earlier developmental stage of the sample accompanies the large changes in many other physiological domains that may be affecting the presentation of symptoms that are similar to environmental sensitivity. An Adult sample might therefore show different associations, when the phenotype is more stable and other extreme biophysical changes of adolescents are not emphasised.

4.4.5 Future research

Future studies should aim to address the limitations of the current study as noted in the previous section, by including larger sample sizes to provide better-powered studies for genome-wide approaches. Since this was the first comprehensive study of genetics of environmental sensitivity, the results may be considered preliminary and future studies are required to further validate the findings of the current study.

The current study only examined common SNPs, but it is likely that other types of genetic factors are involved. Future studies could use other DNA structural variations such as CNVs, insertions/deletions or rare variants to study the genetics of environmental sensitivity. The current study examined only main effects of genes on environmental sensitivity, and future studies would benefit from using a longitudinal Genome-wide x E design for this purpose.

Importantly, while the genetic associations with environmental sensitivity implicate these genes as sensitivity genes, future studies could test their implied association from a different perspective, by testing whether they do indeed moderate the impact of environmental influences for better and for worse. Finally, while the current study showed that the genetic basis of environmental sensitivity is polygenic, and that pathways other than those related to brain and serotoninergic and dopaminergic are worth studying, the biological consequences of the SNPs that explain 3% of variation in environmental sensitivity are as yet unknown. Future follow up studies could examine how the SNPs from significant PGS of different traits may relate to the biology and potential mechanisms of sensitivity.

4.4.6 Conclusions

The results of the analyses in the current chapter included several novel findings in the genetics of environmental sensitivity. The exploratory genome-wide approaches identified potential novel sensitivity genes, including *LOC101926964, NFE2L2,* and *DHX35* from GWAS meta-analysis, and *LBX1* from the gene-based analyses. The gene-set analysis identified two potentially relevant gene-pathways *(*PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY; MIKKELSEN_ES_ICP_WITH_H3K4ME3_AND_H3K27ME3) for environmental sensitivity, with biological processes implicated in embryonic development, cell differentiation and apoptosis. The polygenic score analysis showed strong support for the polygenic nature of environmental sensitivity and confirmed the findings from twin

model analysis in **Chapter 3**, by showing significant genetic correlations between extraversion, neuroticism, anxiety and depression, and first evidence of genetic correlation between autism, openness and subjective wellbeing. The polygenic score results provide encouraging evidence for future investigations of the genetics of environmental sensitivity using polygenic genome-wide approaches

Chapter 5

Genetic sensitivity and response to positive and negative environmental influences

5.1 Introduction

The results from **Chapter 4** identified molecular genetic factors associated with individual differences in sensitivity to environmental influences. The next step, after identifying *what* genetic factors underlie environmental sensitivity, is to examine *how* they operate as individual-specific characteristics to influence mental health and wellbeing outcomes. As detailed in **Chapter 1,** differential susceptibility theories suggest that sensitivity functions in a "*for better and for worse manner".* Specifically, more sensitive individuals respond more negatively to adversity, but also benefit more from positive features of the environment. The implication of this pattern of interaction with the environmental context is that heightened sensitivity increases the risk of psychopathology in adverse contexts, but would also be associated with more positive outcomes in response to environmental contexts that promote wellbeing. Genetic sensitivity therefore functions in a *for better and for worse manner* (Belsky, Fearon, & Bell, 2007).

The main aim of the current chapter is therefore to examine this proposed function of sensitivity. Specifically, the current chapter examines how genetic sensitivity moderates the effects of environmental factors on clinical depression and psychological distress and response to therapeutic psychological interventions. These outcomes are measured in three separate studies with different designs, using a polygenic score-x-environment interaction paradigm. The first study examines the interaction between genetic sensitivity and childhood psychosocial environmental quality in predicting psychological distress across the life span in adulthood, in a prospective longitudinal cohort study. The second study examines the interaction between genetic sensitivity and environmental factors such as childhood maltreatment and recent stressful life events on risk for clinical depression, in a cross-sectional case/control design. The third study examines the interaction between genetic sensitivity and three types of Cognitive Behavioural Therapy (CBT) treatments in predicting reduction of paediatric anxiety symptoms.

The following section includes a detailed review and evaluation of the GxE literature that have examined the moderating function of genetic sensitivity on environmental exposures on a range of mental health outcomes, according to the differential susceptibility theories.

5.1.1 Review of environmental sensitivity GxE research

The GxE literature in support of the hypothesised moderating action of genetic sensitivity can be categorised into two main groups. The first group includes earlier GxE studies, the results of which provide evidence for environmental sensitivity, but which have not been conducted under the differential susceptibility theories framework from the outset. The second group includes more recent GxE studies (from 2009 onwards), which have been conducted from the outset under the differential susceptibility framework and are specifically set out to test the proposed GxE function of environmental sensitivity. The first group of studies has been used as initial evidence for differential susceptibility. However, the design of early GxE studies (e.g. not having a full range of the environmental variable from the negative to the positive end of the spectrum) naturally limits the interpretation of findings as evidence for a differential susceptibility model. The literature review in this section therefore concentrates on recent GxE studies that have been conducted under the differential susceptibility framework including an environmental variable that ranges from negative to positive.

As discussed in detail in **Chapter 4**, the majority of GxE studies in environmental sensitivity include testing the moderating effects of one or several candidate sensitivity genes, usually from serotoninergic or dopaminergic systems, on a wide range of environmental factors on outcomes including both normal developmental outcomes and psychopathology (e.g. literacy, depression). Meta-analyses of the studies with serotonin transporter gene variants (van IJzendoorn et al., 2012) and dopamine-related genes (Bakermans-Kranenburg & van IJzendoorn, 2011) have found GxE interaction patterns consistent with differential susceptibility theories. For example, the *5-HTTLPR* s-allele has been associated with higher neuroticism in the context of negative life events, but also found to be associated with lower levels of neuroticism in the context of positive life events (Pluess et al., 2010). Elsewhere, the same genotype has been found to moderate *for better and for worse*, the impact of parenting practices on children's positive affect (Hankin et al., 2011), and of perceived racial discrimination and child maltreatment on conduct problems and antisocial behaviour (Cicchetti et al., 2012). In other studies with *DRD4* as marker of sensitivity, higher genetic sensitivity (*DRD4* 7-repeat genotype) was associated with higher inattention in the context of insensitive early maternal care, but also with lower levels of inattention in the context of more sensitive maternal care (Berry et al., 2013), with development of social competence in interaction with quality of child-care (Belsky & Pluess, 2013b), and pro-social

behaviour (Knafo et al., 2011) and children's externalizing behaviour (Bakermans-Kranenburg et al., 2008) in interaction with parenting practices.

Other studies have used an aggregated measure of genetic sensitivity by considering several rather than single candidate genes, and report similar findings. For example, using longitudinal data from a sample of over 500 individuals, Simons et al. (2011) found that functional polymorphisms in the dopamine receptor gene (*DRD4*) and serotonin transporter gene (*5-HTTL*) moderated the effects of positive (i.e. supportive parenting, religious participation, neighbourhood informal social control, and school involvement) and adverse (i.e. harsh parenting, racial discrimination, neighbourhood victimization, and violent peers) social conditions on aggression in early adulthood. The interaction pattern supported a differential susceptibility perspective, such that heightened genetic sensitivity was associated with more aggression in adverse environmental contexts, and less aggression in more positive contexts. In another study, Dalton et al. (2014) examined the effects of Brain-Derived Neurotrophic Factor (*BDNF*) and *5-HTTLPR,* by comparing the effects of family environment on depression scores (N=363) as a function of a cumulative sensitivity genotype, defined as presence of both, either, or neither sensitivity alleles (i.e. *BDNF* Met allele and *5-HTTLPR* short allele). They found that genetic sensitivity interacted with family environment quality to predict depression among males and females at age 15. The pattern of interaction supported a differential susceptibility model, such that those with sensitivity alleles experienced more or less depressive symptoms depending on quality of the family environment. They also found that after age 15, the interaction was only predictive of depression among females, and reflected a diathesis-stress model of gene-environment interaction.

Although valuable in establishing an association between genotype, environmental factor and the outcomes, all of the studies reviewed so far have a correlational design. Experimental GxE designs are the ideal way for inferring causality of the effects, however, they pose considerable ethical issues were researchers to expose some individuals to adversity while allocating others to nurturing conditions. However, experimental designs that consider treatment response can provide an ethical and powerful way to test whether the effects of environmental exposures (treatment type) on the outcome (treatment response) vary as a function of genotype. In addition to inferences on causality, the experimental GxE design results in lower measurement error, requires fewer participants, and has greater statistical power than correlational studies (McClelland & Judd, 1993). GxE research in environmental sensitivity has

indeed taken advantage of the benefits of using this design. For example, Chhangur, Weeland, Overbeek, Matthys, and Orobio de Castro (2012) examined whether a polygenic score derived from five dopaminergic gene variants (*DRD4*, *DRD2*, *DAT1*, *MAOA*, and *COMT)* moderated the efficacy of a parenting intervention program for children's behavioural problem in a randomized controlled trial design (*N*=341 families with children). They found that boys carrying 3–5 sensitivity gene variants showed the largest reduction in behavioural problems at both post treatment and 8-month follow up, compared to less genetically-sensitive children.

A meta-analysis of experimental studies in environmental sensitivity provided further support for this hypothesis (van Ijzendoorn & Bakermans-Kranenburg, 2015). This meta-analysis, which consisted of 22 experimental GxE studies (*N*= 3,000) showed that both the exon 3 *DRD4* VNTR and *5-HTTLPR* moderated response to interventions for a range of developmental outcomes including externalising problems, internalising behaviours, and cognitive development. The authors found that while the effect sizes for the interventions were moderate and significant for individuals with environmental sensitivity genotypes, for those with the alternative genotypes, the interventions were no more effective than the control condition. Though encouraging, there is an important confound in the experimental studies of environmental sensitivity, whereby the majority of studies consist of interventions aimed at parents, in order to examine the effects of subsequent change in the environment on the child's behaviour as a function of the child's genotype. What is not accounted for in such studies is the genetic relationship between the parent and child, which may mean the more genetically sensitive children also have more genetically sensitive parents who benefited more from the intervention, and thus impacted the outcome indirectly that way.

While not a test of genetic sensitivity, other experimental studies that have used the phenotypic measure of sensitivity, have also found similar results. For example, a study by Pluess and Boniwell (2015) examined response to a school-based resilience-promoting program aimed at reducing depressive symptoms in adolescents. They found a main effect of treatment for all individuals at 6 months follow up, but that the reduction in depression symptom was only significant at 12 months follow up for those adolescents who were more sensitive (higher scores on the highly sensitive personality questionnaire). In another recent study, Nocentini et al. (2018) tested whether individual differences in environmental sensitivity predicted treatment response in a large randomized controlled trial (*N*=2,042) of an anti-bullying intervention in school

settings. They found that the intervention effect on victimization and internalising symptoms were moderated by environmental sensitivity, such that highly sensitive boys showed significantly larger reduction in victimization and internalizing symptoms than less sensitive boys.

The majority of the studies reviewed so far have used single or multiple candidate genes to index genetic sensitivity in a correlational or experimental design. Using a genome-wide PGS x E approach (gPGS x E), where the PGS is derived of genome-wide variants has been applied in several studies on depression (e.g. Mullins et al., 2016; Peyrot, Wouter J et al., 2014), but is yet to be employed in environmental sensitivity research, except for one study to date by Keers et al. (2016). Compared to candidate GxE, this approach captures the inter-individual variation in the genetic component across the whole-genome, rather than indexing variation as a function of a single variant; therefore should be able to explain more of the variation in the GxE model. In the only genome-wide study of environmental sensitivity, Keers et al. (2016), used a gPGSxE approach to test environmental sensitivity in a treatment response design. In this study, the authors first obtained a score of environmental sensitivity, by calculating differences in scores of emotional problems in MZ twin pairs. This score was then used as an outcome in a GWAS. Using the summary statistics from this GWAS, a PGS of environmental sensitivity was constructed in a separate sample of children undergoing psychological treatments for anxiety disorders. The authors showed that participants' reduction in anxiety symptoms in response to three types of CBT (Individual, group or guided self-help) differed as a function of their PGS. The results supported the differential susceptibility theories, whereby higher genetic sensitivity was associated with more discriminant reaction to the type of treatment received, with better response to individual CBT versus guided self-help, compared to less genetically sensitive individuals whose response did not differ across treatment types. While an innovative and intelligent approach was taken in this study to index genetic sensitivity, the one limitation may be that the PGS reflects more genetic sensitivity to environmental factors that are specifically involved in depression, rather than genetic sensitivity to all types of environmental influences.

Overall, the reviewed literature provides evidence to support the proposition that environmental sensitivity moderates the impact of environmental influences on a range of mental health and related outcomes, with heightened sensitivity inferring greater risk for negative outcomes, but also more beneficial outcomes in more positive contexts. It

would be remiss, however, to not mention that some studies conducted within this framework have failed to find the hypothesised interaction pattern (e.g. see Belsky et al., 2014; Kochanska et al., 2011). Additionally, there are some limitations and gaps in the research reviewed so far, as will be the focus of the next section.

5.1.2 Limitations of GxE research on environmental sensitivity

The first limitation is the almost exclusive use of candidate genes to index genetic sensitivity, whereby all studies so far (expect for one by Keers et al. (2016)) have examined only one or several selected candidates. Briefly, the main limitation of this approach is that the effect of single or multiple variants on a phenotype, whether as a main effect or in an interactive model, is deemed to be too small to be biologically meaningful (see **Chapter 4, Section 4.1.3** for a more detailed discussion). Using a polygenic score that summarises genetic differences using hundreds to thousands of genetic variants can better account for the more complex biological factors that are likely to be involved in interaction with the environmental influences that bring about a particular outcome (e.g. for depression see Mullins et al., 2016; Peyrot, W. J. et al., 2014).

The second limitation is related to how genetic sensitivity is identified. While the GxE studies in the field have so far identified certain genetic variants as genetic sensitivity candidates based on their pattern of interaction with environmental influences, none of these candidate genes have been previously examined for their association with phenotype of sensitivity. As per the results of analyses in **Chapter 4**, these previously strong candidate genes for sensitivity were not found to be associated with the only available phenotypic measure of sensitivity. These candidate genes may not therefore strictly reflect general sensitivity to environments, especially considering that much of these sensitivity genes have been consistently studied in the context of specific disorders (e.g. *5-HTTLPR* and depression; *DRD4* and externalizing behaviour; *COMT* and psychosis), and perhaps reflect genetic sensitivity to the specific environments that are relevant to the specific disorder. Therefore, constructing a GxE model, in which the genetic score reflects general sensitivity to a wide range of environmental factors, captured through the phenotype of sensitivity, may provide a more accurate examination of how genetic sensitivity relates to mental health outcomes.

The third limitation relates to the lack of epidemiological/life-course studies of sensitivity. Although several studies have used a longitudinal design, via repeated

measurements across 3 to 4 years in specific developmental periods (e.g. Dalton et al., 2014), there are to date, no GxE studies of environmental sensitivity across life span, bar one by Keers and Pluess (2017). The cross-sectional or limited longitudinal design of the current studies means that so far our insight into if and how the effects of genetic sensitivity may change across the life span is very limited. In the only life span study of genetic sensitivity, Keers and Pluess (2017) used a PGS of environmental sensitivity from nine candidate genes, and childhood and adulthood material environment, to predict psychosocial distress in adulthood in a longitudinal cohort from 7 to 50 years old. Using linear mixture models, the authors reported that there was no significant gene by childhood environment or gene by adulthood environment interactions on psychological distress. However, they did find significant evidence for GxExE in predicting adulthood psychological distress. Specifically, for children with a low genetic sensitivity, childhood environment had little effect on their sensitivity to stress in adulthood. However, genetically sensitive children who experienced a positive childhood environment were *less* sensitive to the depressogenic effects of a poor environmental quality in adulthood. These findings suggest that sensitivity in adulthood may be a product of both genetic factors and early environment and future studies of sensitivity may need to take a developmental approach, taking into account both childhood and adulthood environments. Nevertheless, the results of this study are affected by the limitations discussed above. That is, that they index genetic sensitivity via a handful of candidate genes with evidence from GxE studies, but no prior evidence of a direct association with the environmental sensitivity phenotype.

The final limitation relates to the paucity of environmental sensitivity research with clinical outcomes. Much of previous GxE studies of environmental sensitivity have examined mental health outcomes using community samples and disorder symptoms rather than clinical diagnosis. It is therefore unclear how genetic sensitivity may relate to clinically-ascertained outcomes, either in terms of development of the disorder or treatment response. It is important to make a distinction between clinical outcomes versus symptoms, because it is possible that heightened sensitivity in adverse contexts impairs functioning to some extent, as for example reflected in elevated levels of depressive symptoms, but not to the extent that would contribute to the development of a clinically distinct disorder such as major depression diagnosis. In order to be able to extend the relevance of genetic sensitivity to psychopathology, empirical test of its association with clinically diagnosed disorders are therefore essential.

5.1.3 Aims

The main aim of the current study was to examine how genetic sensitivity interacts with environmental factors to influence the risk of psychopathology and response to psychological intervention. This was tested using a GxE interaction design in three separate studies. The first study examines the interaction between genetic sensitivity and childhood psychosocial environmental quality in predicting psychological distress across life span in adulthood, in a prospective longitudinal cohort study of 2,863 individuals from age 7 to 50. The second study examines the interaction between genetic sensitivity and environmental factors such as childhood maltreatment and recent stressful life events on risk for major depression, in a cross-sectional case/control design study of 2,434 individuals. The third study examines the interaction between genetic sensitivity and three types of Cognitive Behavioural Therapy (CBT) treatment in predicting reduction of paediatric anxiety symptoms in an experimental design study of over 900 individuals.

These studies attempt to address the limitations and gaps in research identified in **Section 5.1.2**. To do this, all three studies used a genome-wide PGS of sensitivity developed in the previous chapter, rather than candidate genes to index genetic sensitivity. In addition, the PGS was derived from a validated measure of the environmental sensitivity phenotype, which captures general sensitivity to all environmental influences, rather than sensitivity to a measured environmental factor, as in previous GxE studies. Finally, a life course approach was taken in Study 1, in order to study how genetic sensitivity interacts with environmental factors to influence probability of psychopathology across life span.

According to differential susceptibility theories, it is hypothesised for Study 1 and 2, that genetic sensitivity will infer a greater risk of psychopathology in adverse contexts, but that it is also associated with decreased risk in more positive contexts. A similar interaction pattern is expected to be found in Study 3, with polygenic score of sensitivity moderating response to treatment, with higher genetic sensitivity showing enhanced treatment response.

5.2 Methods

Three data sets were used to examine the aims of the current chapter. The methods and analytical approaches for each of the three studies are presented in separate sections. All statistical analyses were carried out using STATA 12 (StataCorp, 2011).

5.2.1 Study 1: The National Child Development Study (NCDS)

5.2.1.1 Study 1: Sample, measures and procedures

Data: NCDS is a continuing, multidisciplinary longitudinal British birth cohort study. The study followed 18,558 babies born in a single week in 1958, in England, Scotland, and Wales. The study collected information on physical development, education, social and economic circumstances, family life, health, welling and social participation at 9 time points at ages 7, 11, 16, 23, 33, 42, 46, 50, and 55 years. During the follow-ups at ages 7, 11 and 16 years, the original birth cohort was augmented by including immigrants born in the relevant week, as identified from school registers. Detailed information on ethics approval and informed consent across the different data collection waves is available elsewhere (Shepherd, 2012).

Genetic data was available from several genome-wide association studies of different subsamples of the NCDS cohort, including the Wellcome Trust Case Control Consortium's Wave 1 and 2 controls, and the Type 1 Diabetes Genetics Consortium study, genotyped on Illumina and Affymetrix platforms. For the current study, in order to maintain compatibility with the other GWAS data used for polygenic scoring, only genotyped data from Illumina platform, imputed to human genome build 37 were used.

Sample: The current study included a subsample of 2,919 individuals from the NCDS data for whom genotype data were available. Following genotype data quality control procedures, 56 individuals were removed, leaving a final sample of 2,863 individuals (male=1,478, female=1,385). More detailed descriptive statistics of the sample for each age group are included in **Section 5.3.1.1.**

Measures: The measures in the current study included psychological distress in childhood and adulthood, index of childhood psychosocial environmental quality, and the PGS of sensitivity derived from the meta-analysed GWAS results in **Chapter 4**.

Psychological Distress in childhood was measured via the depression scale of Bristol Social Adjustment Guides (BSAG; Stott, 1963), collected at ages 7 and 11. BSAG is a

four-page booklet of 250 descriptions of behaviour, where teachers select the items that best describe the child. By summing up groups of items, a quantitative measure of child's behaviour disturbances in several domains including depression, anxiety, hostility and restlessness are obtained. The depression scores were used in the current study to measure psychological distress in childhood. For adulthood measure of psychosocial distress, the Malaise Inventory (Rutter, Tizard, & Whitmore, 1970) was used at ages 23, 33, 42 and 50. Of the original 24 items in the inventory, nine (items 2, 3, 5, 9, 12, 14, 16, 20, and 21) were available at each of the adult time points. These items covered symptoms of emotional disturbance and associated physical symptoms (e.g. "Do you feel tired most of the time?" "Do you often feel depressed?" "Are you easily upset or irritated?"). Items were rated as 0=No and 1=Yes, and a total score of overall psychological distress was obtained by summing up all items for those individuals with over 80% completeness rate for all 9 items. The total score was standardized prior to the analyses. The scale showed acceptable reliability at all ages (Cronbach alphas: 0.6, 0.73, 71, and .78 at 23, 33, 42, and 50 years, respectively).

Psychosocial environment quality was indexed via a composite score of questions on socio-demographic and psychosocial environment during childhood (ages 7, 11, and 16) and adulthood (ages 23, 33, 42, 50). The Childhood environmental quality index included 5 questions at ages 7,11 and 16. The questions included questions such as whether the mother reads to the child (age 7), whether mum takes child for walks (age 11), Child gets on with mother/father/siblings (age 16), Dad's involvement in parenting, and mother/father's interest in child's education (all ages). All items were rated on a scale of 1= rarely/low to 3= always/high. A total score of environmental quality at each age was obtained by summing up all items for those individuals with over 80% completeness rate for all 5 items. A score of overall childhood environmental quality was obtained by calculating the average score across ages 7, 11 and 16 for each individual. The scores were standardised for the analyses. For adulthood environmental quality index, the measure was composite score of 5 questions on participant's employment status, partnership status, accommodation tenure (owner of property or rented), number of bedrooms, and social class (current or most recent occupation), rated on a scale of 0 to 1. A total score of adult socioeconomic environmental quality was obtained by summing up all items for those individuals with over 80% completeness rate for all 5 items. The scores were standardised for the analyses. Higher scores on either index indicate higher quality of the childhood or adulthood environment.

Polygenic score of sensitivity was obtained from NCDS GWAS data, using summary statistics from meta-analysed GWAS of environmental sensitivity (1,035 individuals and 2,422,121 SNPs) as detailed in **Chapter 4.** The initial NCDS genotype data included 6,662,419 SNPs and 2,919 individuals. The genotype data for the current study were subjected to the same quality control procedure as described in **Chapter 4, Section 4.2.2.2.** This included filtering out the data for Indels and rare SNPs (Maf < .01), per-SNP and per-individual missingness rates (> 1%), SNPs with deviation from HWE ($p < 1x10^{-6}$), IBD outlier individuals (%IBD > .1875), and genome-wide heterogeneity individual outliers. The NCDS genotype data after all quality control steps included 5,854,454 SNPs and 2,863 individuals. Of the 2 million SNPs in the base dataset, 1,931,667 SNPs were available in NCDS data. Polygenic scores for each individual were obtained from SNPs in 69,311 clumps, at nine p-value thresholds (P_T=. 001, .01, .05, .1, .2, .3, .4, .5, and 1), using the same settings as described in **Chapter 4, Section 4.2.2.4**. Principal components of the genetic data were obtained using PCA in EIGENSTRAT, according to the same protocols as described in **Chapter 4, Section 4.2.2.2.** The PCA identified 3 PCs to be included in the GxE analysis to control for population stratification effects. The genotype quality control and PCA procedures are presented in **Figure 5.1a, 5.1b** and **5.1c**.

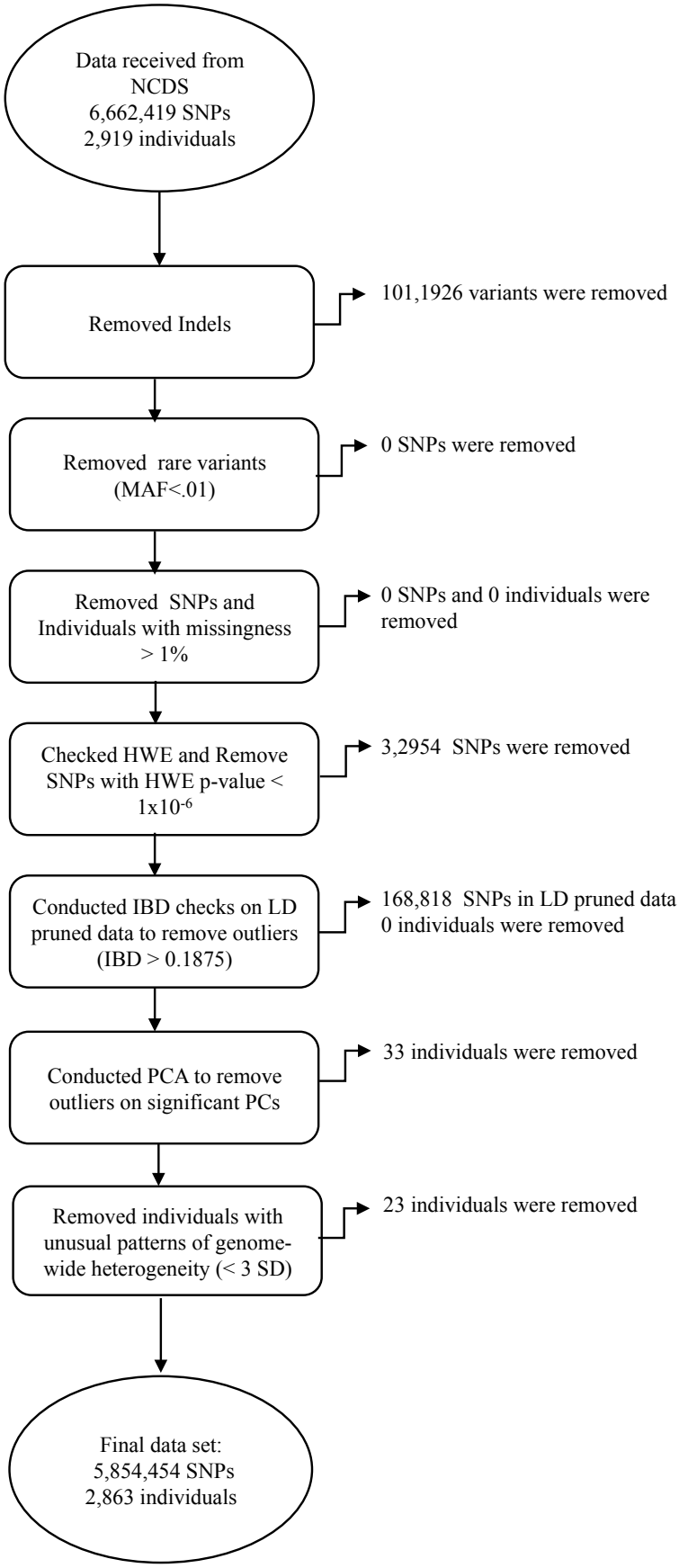


Figure 5.1a Genotype data quality control process (Study 1)

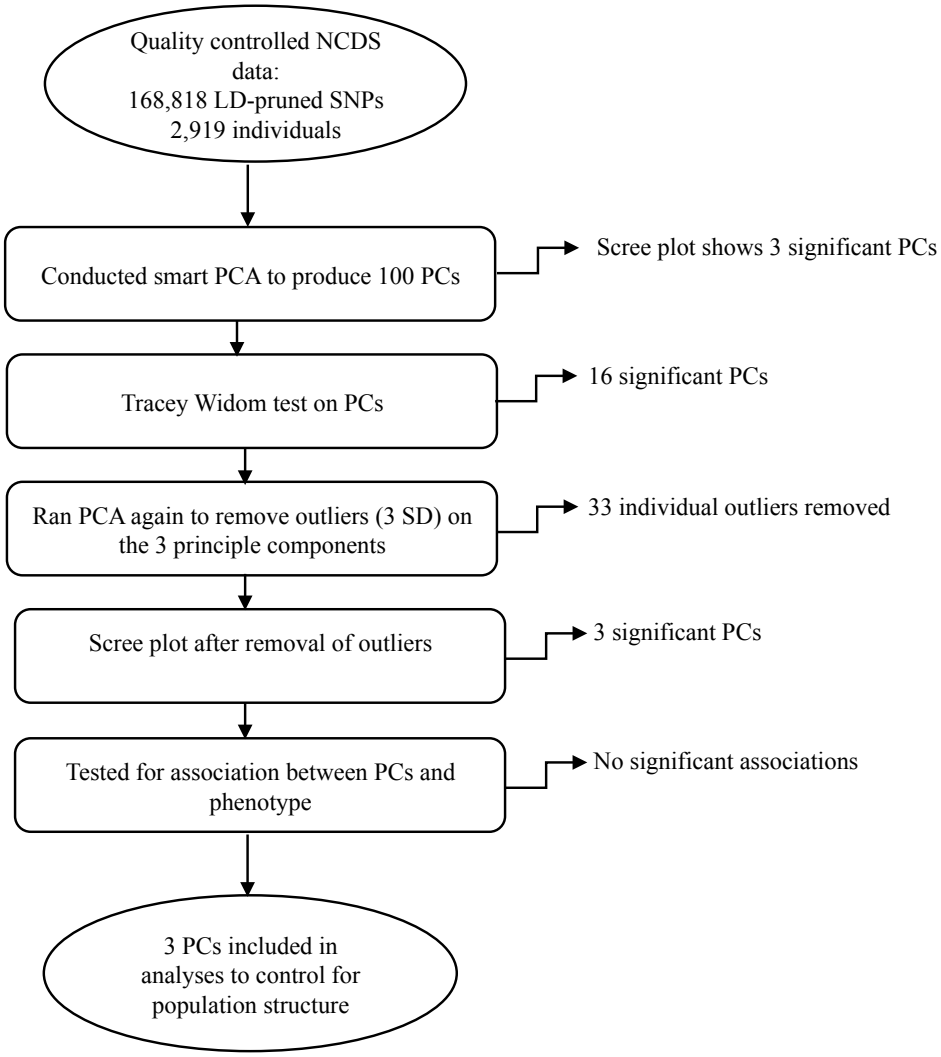


Figure 5.1b PCA analysis process (Study 1)

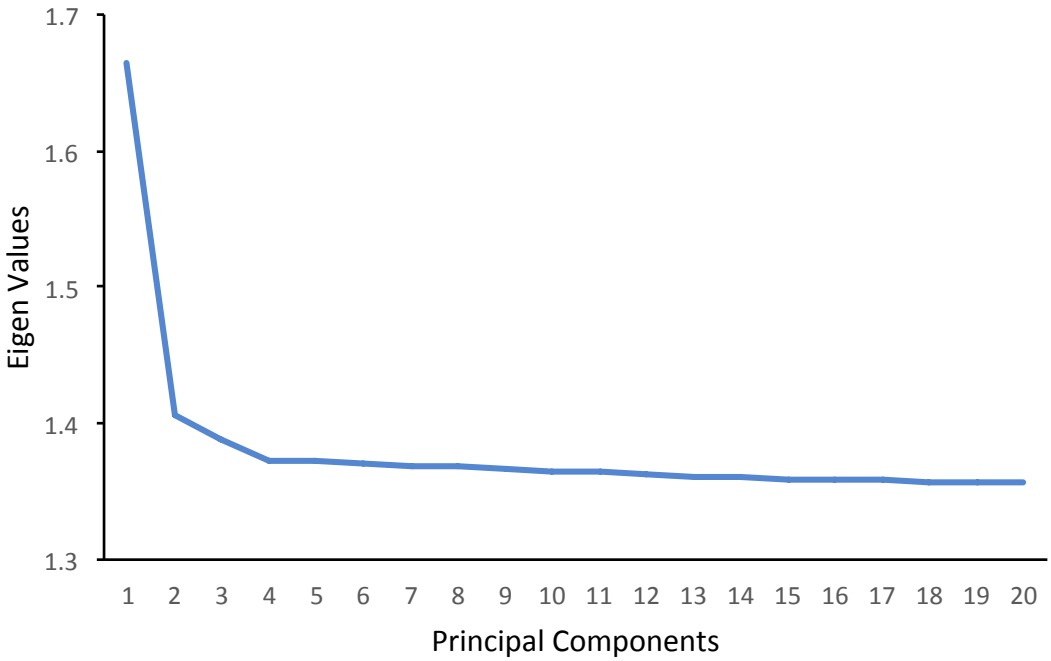


Figure 5.1c Scree plot of PCs after removal of individual outliers (Study 1)

5.2.1.2 Study 1: Data analysis

Analytical approach: The study design was longitudinal, with psychological distress at 6 time points as the outcome, two environmental factors (childhood psychosocial environment at 3 time points, and adult psychosocial environment at 4 time points), and 9 polygenic scores at each time point. The effects of childhood psychosocial environment and PGS on psychological distress across adulthood were examined using linear mixed effect models fitted with full maximum likelihood. By modeling the relatedness between repeated measures in the same individual as random intercepts, these models allowed data from each time point to be included simultaneously and to estimate overall effects of the childhood predictor across adulthood. The following parameters were included as fixed effects in the models: Childhood environment quality at age 7, 11, 16 or overall childhood environment (centred at mean), PGS (centered at mean), PGS x environment interaction term, principal components (3 PCs centered at mean) to account for population stratification effects, adult environment (centred at mean) to account for the concurrent effect of the environment, sex, and time (in decades) to account for the effects of time. All models included the random effects of individual to account for correlations between repeated measures from the same participant. In order to rule out gene-environment correlation (rGE) confounding the GxE effects, linear regression analyses were conducted to examine the association between PGS and environmental factors, in a model that included the environmental factor as the outcome and PGS as the predictor, with sex and 3 PCs as covariates.

Data analysis steps: First, the main effects of the environmental factors and the polygenic score on adulthood psychological distress were examined. This was done by conducting a series of linear mixed effect models with psychological distress as the outcome, each of the environmental factors (environmental quality at age 7, 11, 16, overall childhood environment or concurrent adult environment) as a fixed effect. Similar models were used to test each of the polygenic scores of environmental sensitivity on psychological distress. All models included sex and time as fixed effect covariates and individual as a random effect. Polygenic analysis also included the first 3 PCs to control for the effects of population stratification. Second, the moderating effects of PGS on the link between childhood environmental quality and psychological distress in adulthood was examined. This was done by conducting a series of linear mixed effect models, with psychological distress as the outcome and the fixed effects of childhood environment, PGS, and a PGS by childhood environment interaction term as predictors.

Models were repeated for each childhood environment variable (age 7 or 11 or 16 or overall childhood environment) and each PGS. All models also included concurrent adult environment, sex, time and the first 3 PCs as fixed effect covariates. Third, we explored whether the PGS moderated the effects of concurrent environmental quality on psychological distress. This was done by conducting a series of linear mixed effect models with psychological distress as the outcome, and the fixed effects of concurrent environment, PGS and a PGS by concurrent environment interaction term. All models also included overall childhood environment, sex, time and the first 3 PCs as fixed effect covariates. Any significant interaction effects were followed up using simple slopes analyses, with PGS and environmental factor ± 2 *SD*. Fourth, in order to examine gene-environment correlations, a series of linear regression models were constructed with each of the childhood or adult environmental variables as the outcome and PGS as the predictor. All models also included with sex and 3 PCs as covariates. Finally, post-hoc analyses were conducted to explore whether gene-environment interaction findings differed according to the proximity of the environmental exposure to the outcome. In order to allow for the maximum time between environment and outcome measures these analyses focused on the effects of childhood environment at age 7. Linear mixed models were constructed with psychological distress at ages 7, 11, 23, 33, 42, and 50 as the outcome. Predictors included the fixed effects of psychosocial environment (at age 7), PGS and time and the two and three-way interaction terms between each of these variables (i.e. PGS x time, PGS x environment, time x environment, PGS x environment x time). A significant three-way interaction PGS x time x environment was used to indicate that PGS by environment interactions differed as a function of time. Simple slope analyses were used further probe these three-way interactions on psychological distress. This included repeating the above analyses in a series of linear regression models fitted separately for each time point.

5.2.2 Study 2: RADIANT UK

5.2.2.1 Study 2: Sample, measures and procedures

Data: The data in the current study included genetic and clinical depression data from 3 previously published studies: RADIANT UK, Genome Based Therapeutic Drugs for Depression (GENDEP), and the London site of the Bipolar Affective Disorder Case–Control study (BACC). The RADIANT UK (Mullins et al., 2016) includes cases with recurrent Major Depressive Disorder (MDD) drawn from the Depression Case Control (DeCC) study (Cohen-Woods et al., 2009), and probands from the Depression Network (DeNT) study of affected sibling pairs (Farmer et al., 2004). GENDEP is a prospective pharmacogenetic study of patients with moderate to severe unipolar depression, on a 12-week antidepressant treatment course (Uher et al., 2010). BACCs is a multi-site study of Bipolar Affective Disorder (Gaysina et al., 2009; Lewis et al., 2010). Cases (*N*=1,605) were available from RADIANT and GENDEP studies and controls (*N*= 1064) were available from DeCC and the BACCs study. Recurrent MDD was defined as having at least two episodes of moderate severity, separated by two or more months of remission (World Health Organization, 1993). For cases, the exclusion criteria included personal or family history of other psychiatric diagnoses besides anxiety disorder (Cohen-Woods et al., 2009; Farmer et al., 2004; Uher et al., 2010). For healthy controls, exclusion criteria include first-degree family history of any psychiatric disorder or a score of 10 or more on the Beck Depression Inventory at interview (Beck, Steer, & Brown, 1996; Cohen-Woods et al., 2009). DNA samples were extracted from whole blood from depressed cases, and from blood or buccal swabs from controls, and genotyped on the Illumina Human610-Quad BeadChip, and subjected to an established genotype data quality control procedure (Lewis et al., 2010).

Sample: The sample included a total of 2,669 individuals (1,605 cases and 1,064 controls) from the UK for whom genotype data was also available. Two hundred and twenty-three individuals were removed during genotype data quality control process, leaving a final sample size of 2,434 individuals (1,530 cases and 904 controls). Mean age of the sample was 34 (*SD*= .38), with 65% of the sample being female. Data on Childhood Trauma was available only for a subset of the sample (*N*= 496), with 230 cases and 266 controls. The mean age of the sample was 44 (*SD*= .67), with 65% of the sample being female. The ethnicity of the sample was white European from the UK only.

Measures: The measures in the current study included depression status, stressful life events and childhood maltreatment, and the PGS of sensitivity.

Depression was assessed using the self-report Beck Depression Inventory (Beck et al., 1996), in the DeCC and GENDEP cases, and the Schedules for Clinical Assessment in Neuropsychiatry Interview (Wing et al., 1990) in DeNT. Information was recorded on patients' worst and second worst episodes of depression in the DeCC and DeNT studies and on their current episode in the GENDEP study (Lewis et al., 2010). Controls were screened for life- time absence of all psychiatric disorders using the Past History Schedule (McGuffin, Katz, & Aldrich, 1986)

Stressful Life Events were assessed via the Brief Life Event Questionnaire, which is a shortened version (11 items) of the List of Threatening Experiences Questionnaire (LTE-Q; Brugha & Cragg, 1990), as well as an extra item on childbirth (Farmer et al., 2004). Cases in the DeCC and DeNT studies were asked whether or not they experienced each SLE in the 6 months prior to their worst episode of depression, while GENDEP cases were asked to report on the 6 months preceding the clinical trial (Fisher et al., 2012; Keers et al., 2011). Controls were asked about SLEs in the 6 months prior to their interview. The number of reported SLEs was summed for each individual, and the score was coded as low, medium and high for analyses. Missing information on age at worst episode of depression (233 cases) and age at interview (34 controls) was replaced with the mean age at worst episode or interview as appropriate. In line with Mullins et al. (2016), number of SLEs in cases were adjusted for sex and age, since younger individuals and females reported more SLEs. This was done by using controls as a proxy for the general population to conduct a linear regression of SLEs on age and sex, and then use the regression coefficients to adjust the number of SLEs in depressed cases.

Childhood Maltreatment was measured via the self–report Childhood Trauma Questionnaire (Bernstein et al., 2003). The questionnaire measures frequency and severity of sexual, physical and emotional abuse, and physical and emotional neglect during childhood, using 25 items on a Likert scale. The scores for the specific types of maltreatment ranged from 5 to 25 and overall maltreatment ranged from 25 to 125. For the analyses, overall levels of childhood maltreatment was categorized into none, mild and moderate/severe, according to a definition described previously using this sample (Fisher et al., 2013). CT score was not associated with age or sex, so no adjustment was performed.

Polygenic score of environmental sensitivity was obtained from RADIANT GWAS data, using summary statistics from meta-analysed GWAS of sensitivity (1,035 individuals and 2,422,121 SNPs) as detailed in **Chapter 4, Section 4.3.2.2**, and RADIANT genotype data. The initial RADIANT data included 2,257,734 SNPs and 2,665 individuals (906 males, 1,759 females). The genotype data for the current study were subjected to the same quality control procedure as described in **Chapter 4, Section 4.2.2.2.** This included filtering out the data for Indels and rare SNPs (Maf < .01), per-SNP and per-individual missingness rates (> 1%), SNPs with deviation from HWE ($p<1x10^{-6}$), IBD outlier individuals (%IBD > 0.1875), and genome-wide heterogeneity outlier individuals. The genotype data after all quality control steps included 2,252,052 SNPs and 2,434 individuals. Of the 2 million SNPs in the base dataset, 931,952 SNPs were available in RADIANT data. Polygenic scores for each individual were obtained from SNPs in 56,188 clumps, at nine p-value thresholds (P_T=. 001, .01, .05, .1, .2, .3, .4, .5, and 1), using the same settings as described in **Chapter 4, Section 4.2.2.4**.

Principal components of the genetic data were obtained using PCA in EIGENSTRAT, according to the same protocols as described in **Chapter 4, Section 4.2.2.2**. The PCA identified 3 PCs to be included in the GxE analysis to control for population stratification effects. The genotype quality control and PCA procedures are presented in **Figure 5.2a**, **5.2b** and **5.2c.**

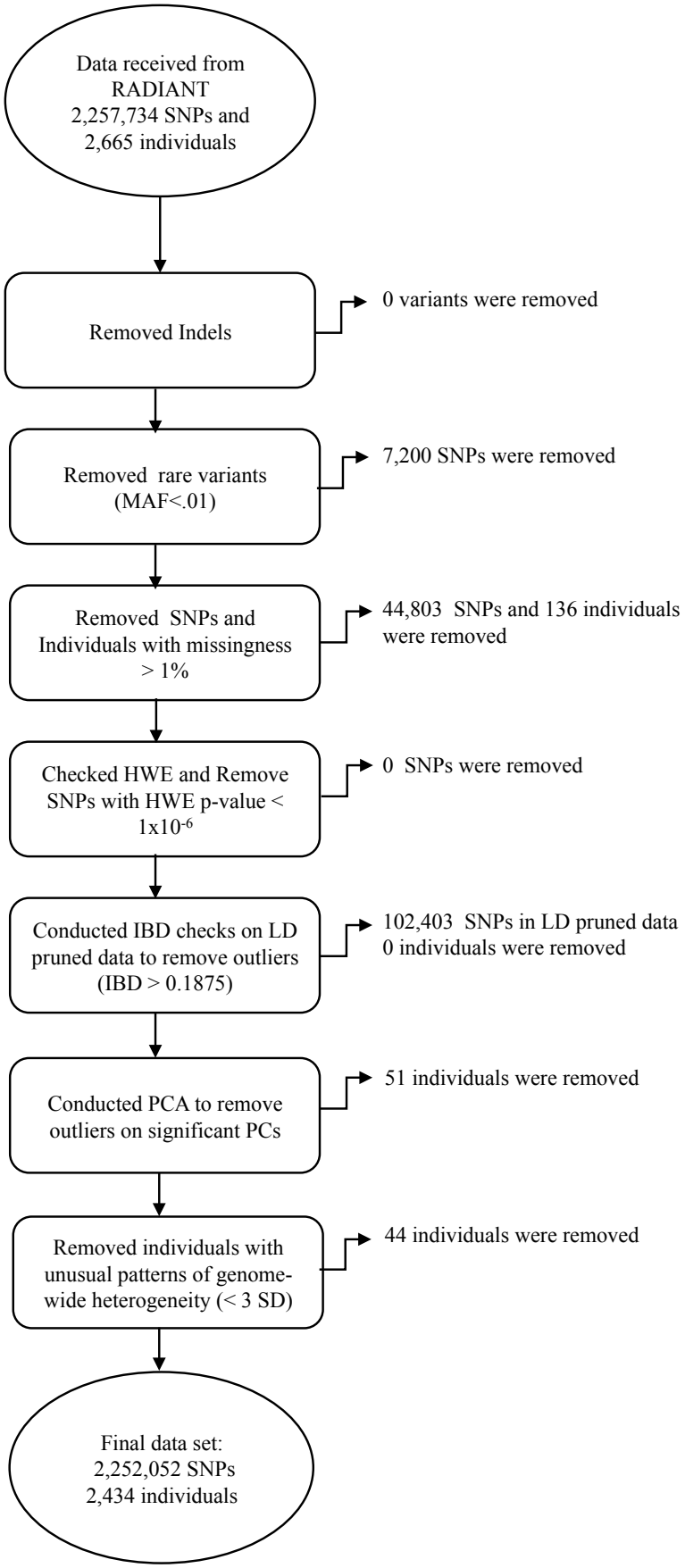


Figure 5.2a Genotype data quality control process (Study 2)

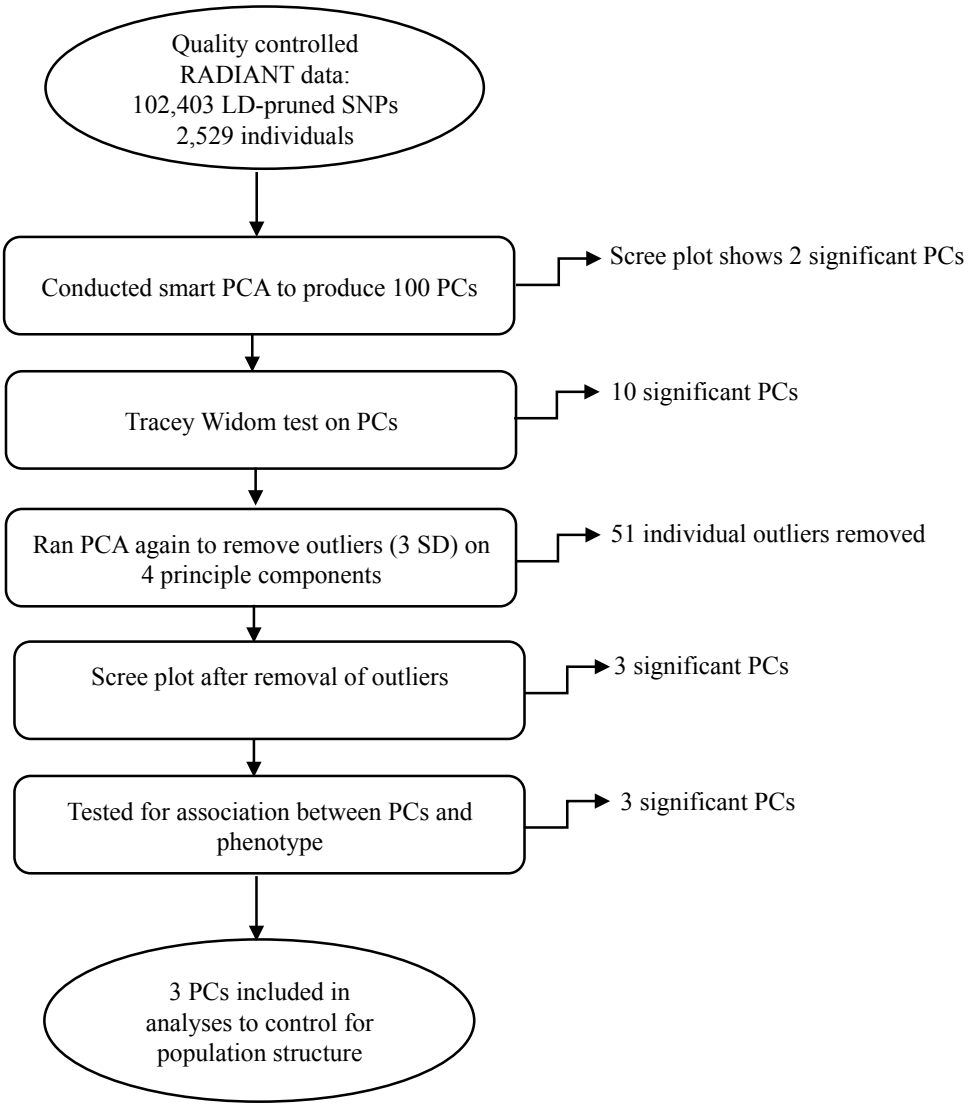


Figure 5.2b PCA analysis process (Study 2)

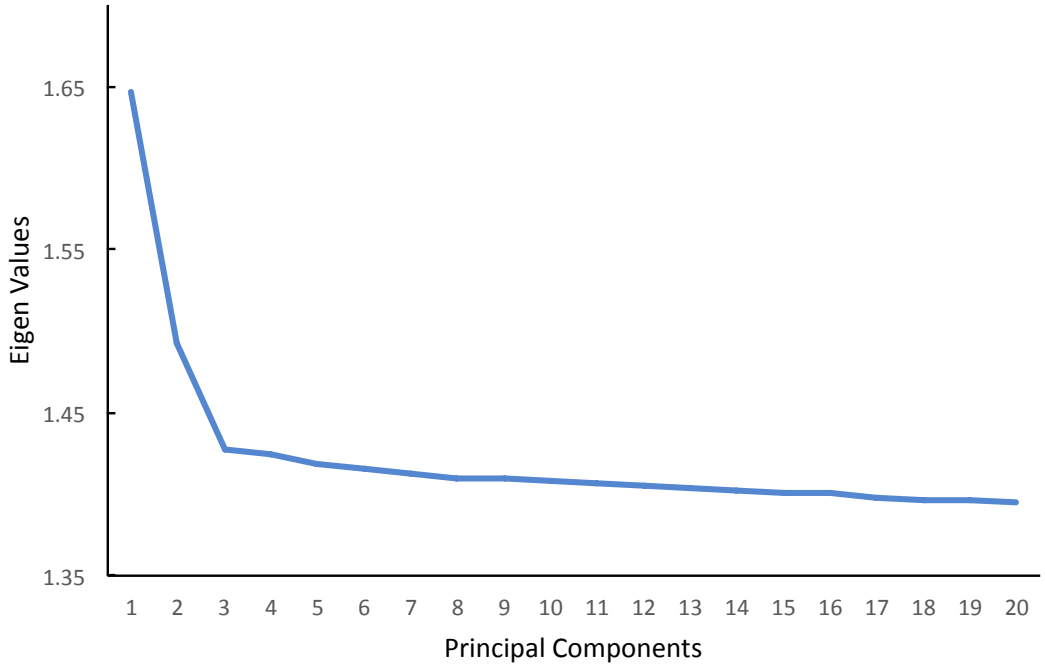


Figure 5.2c Scree plot of PCs after removal of individual outliers (Study 2)

5.2.2.2 Study 2: Data analysis

Analytical approach: The study design was cross-sectional, with outcome as major depression versus control, and childhood trauma (overall score and specific childhood traumas: sexual, physical and emotional abuse, and physical and emotional neglect), stressful life events, and polygenic score of sensitivity as predictors.

A series of logistics regression models were fitted to examine the contribution of each of these predictors to depression case/control status. First, each environmental variable and each PGS were tested for their association with the outcome. Subsequent models tested whether the PGS moderated the effects of the environmental variables by including the main effects of the PGS and environment as well as the interaction between these variables. Analyses were repeated for each of the environmental variables and each PGS. Age (centred at mean) and sex were included as covariates in all models. Models including the PGS also included the first three PCs (centered at mean), to account for population stratification effects. In order to examine if there were any gene-environment correlations, a series of ordinal and linear regressions were used to examine the association between PGS and each of the environmental factors.

Data analysis steps: First, main effects of environmental factors (Childhood Trauma, Stressful Life Events) on depression were examined using logistic regression, in models that included depression as the outcome and the environmental factor, age and sex as predictors. The same was conducted with PGS as the predictor, with PCs 1-3 as additional covariates in the model. Second, the interaction effects of PGS and environmental factors were examined using logistic regression, with depression as the outcome and PGS, environmental factor, their interaction term, age, sex and 3 PCs as the predictors. Significant interaction effects were followed up using simple slopes analyses, with PGS at ± 2 *SD*, and environmental factor at ± 3 *SD*, or at 3 levels (low, medium, high) for ordinal variable of overall maltreatment. Third, gene-environment correlations were examined, using ordinal regression when the outcome was SLEs/overall childhood trauma, and linear regression when the outcome was specific maltreatments, and PGS as the predictor, with sex, age, and 3 PCs as covariates.

5.2.3 Study 3: Genes for Treatment (GxT)

5.2.3.1 Study 3: Sample, measures and procedures

Data: GxT is a multi-site clinical study designed to examine genetic and clinical predictors of response to paediatric anxiety disorders. The initial study comprised data from 1,519 children from 11 sites in 7 countries including Germany, Switzerland, UK, USA, Netherlands, Australia, Norway and Denmark. The inclusion criteria were age (5-18 years old, 94% the sample were 5-13), DSM-IV primary diagnosis of an anxiety disorder and provision of a DNA sample. Exclusion criteria were significant physical or intellectual disability or psychosis. Participants were assessed at baseline for anxiety symptoms prior to receiving individual CBT (mean number of sessions: 11.8,), or group-based CBT (mean number of sessions: 10), or guided self-help CBT (mean number of sessions: 7.3). Their symptoms were then assessed after the completion of therapy (post-treatment), as well as at least once at follow up at 3,6 or 12 months post treatment. Other measures such as parental psychopathology and children's internalising and externalising disorders were also used in the original study, but did not form part of the current study. More information on GxT study is detailed in (Hudson et al., 2015). Genotype data was obtained by genotyping DNA extracted from buccal swabs and saliva, using llumina Human Core Exome-12v1.0 microarrays. Genotype data was subjected to established data quality control procedures for relatedness, data missingness, HWE equilibrium, allele frequency, and genome-wide heterogeneity patterns, according to (Coleman, Lester, et al., 2016) QC procedure. The quality-controlled data was imputed to the December 2013 release of the 1,000 Genomes Project using IMPUTE2. The imputed data contained only SNPs with an information metric > 0.8 and a minor allele frequency >1%.

Sample: The participants in the current study included all of the 980 (444 male, 536 female) participants in the initial dataset with available genome-wide genotype data and at least 1 post-baseline assessment. Following genotype data quality control, 913 individuals (male= 417, female= 496) remained in the final sample, with mean age of 9.83 years old (*SD*= 2.20). Of the 913 participants, 334 had a diagnosis of generalized anxiety disorder (GAD), 188 social anxiety disorder (SoAD), 214 Separation Anxiety disorder (SAD), 102 specific phobias (SP), and 75 "other anxiety" disorders. Other anxiety disorders included panic disorder with and without agoraphobia (*n*= 13), agoraphobia without panic disorder (*n*= 10), obsessive-compulsive disorder (*n*= 33), post- traumatic stress disorder (*n*= 12), selective mutism with a diagnosis of severe

social anxiety disorder (*n*= 1), and anxiety disorder not otherwise specified (*n*= 6). Participants were allocated to one of three treatment groups of individual CBT (*n*= 242), group CBT (*n*= 475), or guided self-help CBT (*n*=196). The ethnicity of the sample based on grandparent's ancestries were 93% white European, 5.26% mixed, 0.81% Arab and Middle Eastern, 0.27% Asian and 0.13% African/Caribbean.

Measures: The measures in the study included severity of the primary anxiety diagnosis (measured at baseline, post treatment and three follow up time points), CBT treatment type and PGS of environmental sensitivity.

Anxiety was assessed via the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV; Silverman & Nelles, 1988) administered in all cites to obtain the anxiety diagnosis, expect for Germany and Switzerland centres where the Diagnostisches Interview bei psychischen Strungen im Kindes- und Jugendalter (Kinder-DIPS; Schneider, Unnewehr, & Margraf, 2009) was administered. Graduate assistants or clinical staff trained in administration of psychological instruments conducted the assessments via structured interviews and according to DSM –IV criteria. Severity was assessed using the clinician severity rating (CSR), which assigns a score of 0 to 8 (absent to very severe). A diagnosis was made when the child met the diagnostic criteria and received a CSR of 4 or more. Diagnostic categories included generalized anxiety disorder (GAD), social anxiety disorder (SoAD), separation anxiety disorder (SAD), specific phobia (SP), and "other anxiety" disorders, which included panic disorder with and without agoraphobia and agoraphobia without panic disorder, obsessive-compulsive disorder, post- traumatic stress disorder, selective mutism with a diagnosis of severe social anxiety disorder, and anxiety disorder not otherwise specified. Symptom severity was assessed at baseline, post-treatment and three follow ups.

Treatment included three types of CBT **(**individual CBT, group CBT, or guided self-help CBT) for anxiety. All treatments were manualised, and treatment protocols across all sites were comparable for core elements of CBT including teaching of coping skills, cognitive restructuring, and exposure. The individual CBT treatment was delivered by qualified clinical psychologists in 1:1 sessions with the participant, group CBT was delivered in a group format with participants, and guided self-help CBT included provision of CBT instructions to parents of the participants.

Polygenic score of sensitivity: PGS scores were obtained from GWAS data, using summary statistics from meta-analysed GWAS of sensitivity (1,035 individuals and

2,422,121 SNPs) as detailed in **Chapter 4, Section 4.3.2.2**. The initial GxT genotype data included 3,017,603 SNPs and 980 individuals. The genotype data for the current study were subjected to the same quality control procedure as described in **Chapter 4, Section 4.2.2.2.** This included filtering out the data for Indels and rare SNPs (Maf < .01), per-SNP and per-individual missingness rates (> 1%), SNPs with deviation from HWE ($p < 1x10\text{-}6$), IBD outlier individuals (IBD > .1875), and genome-wide heterogeneity individual outliers. The genotype data after all quality control steps included 1,998,654 and 913 individuals. Of the 2 million SNPs in the base dataset, 907,788 were available in GxT data. Polygenic scores for each individual were obtained from SNPs in 43,093 clumps, at nine p-value thresholds (*P*T=. 001, .01, .05, .1, .2, .3, .4, .5, and 1), using the same settings as described in **Chapter 4, Section 4.2.2.4**.

Principal components of the genetic data were obtained using Principal Components Analysis (PCA) in EIGENSTRAT, according to the same protocols as described in **Chapter 4, Section 4.2.2.2**. The PCA identified 3 PCs to be included in the GxE analysis to control for population stratification effects. The genotype quality control and PCA procedures are presented in **Figure 5.3a, 5.3b** and **5.3c**.

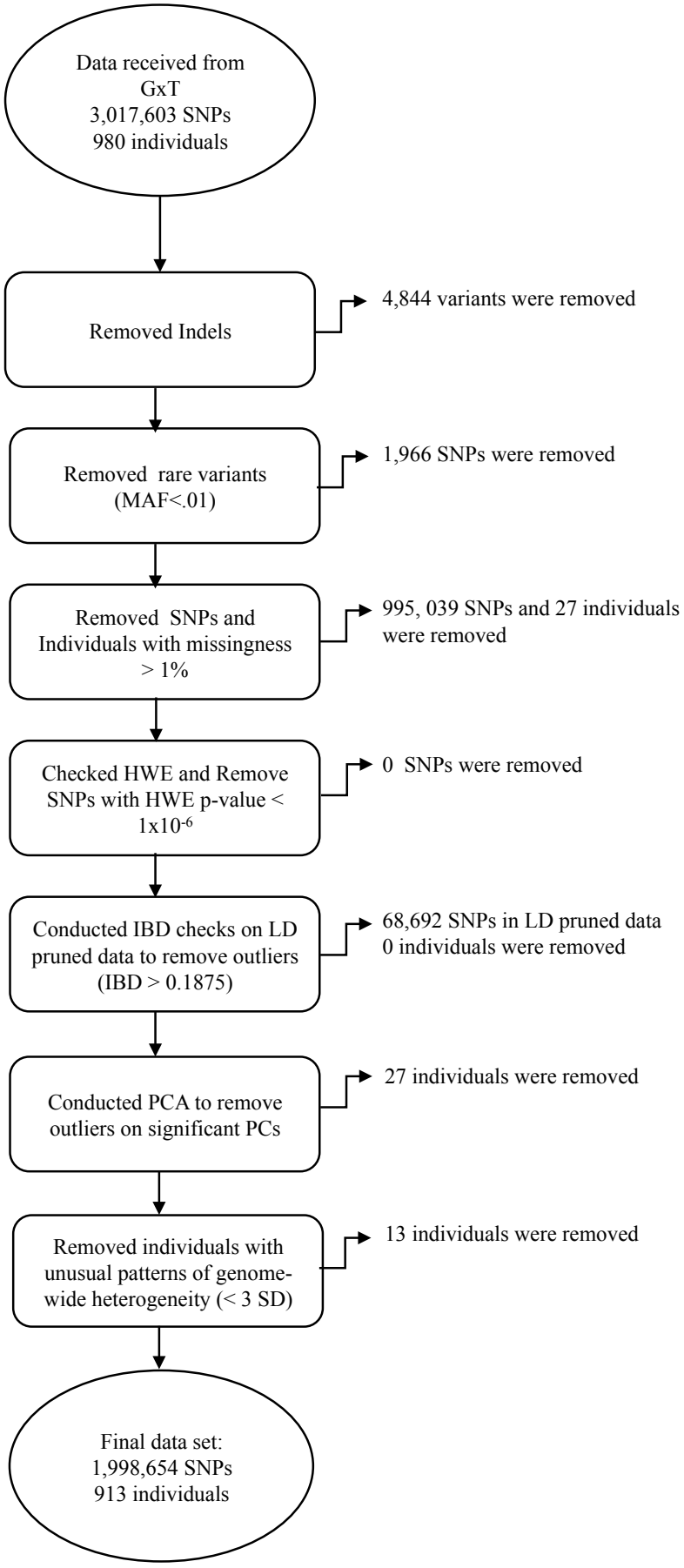


Figure 5.3a Genotype data quality control process (Study 3)

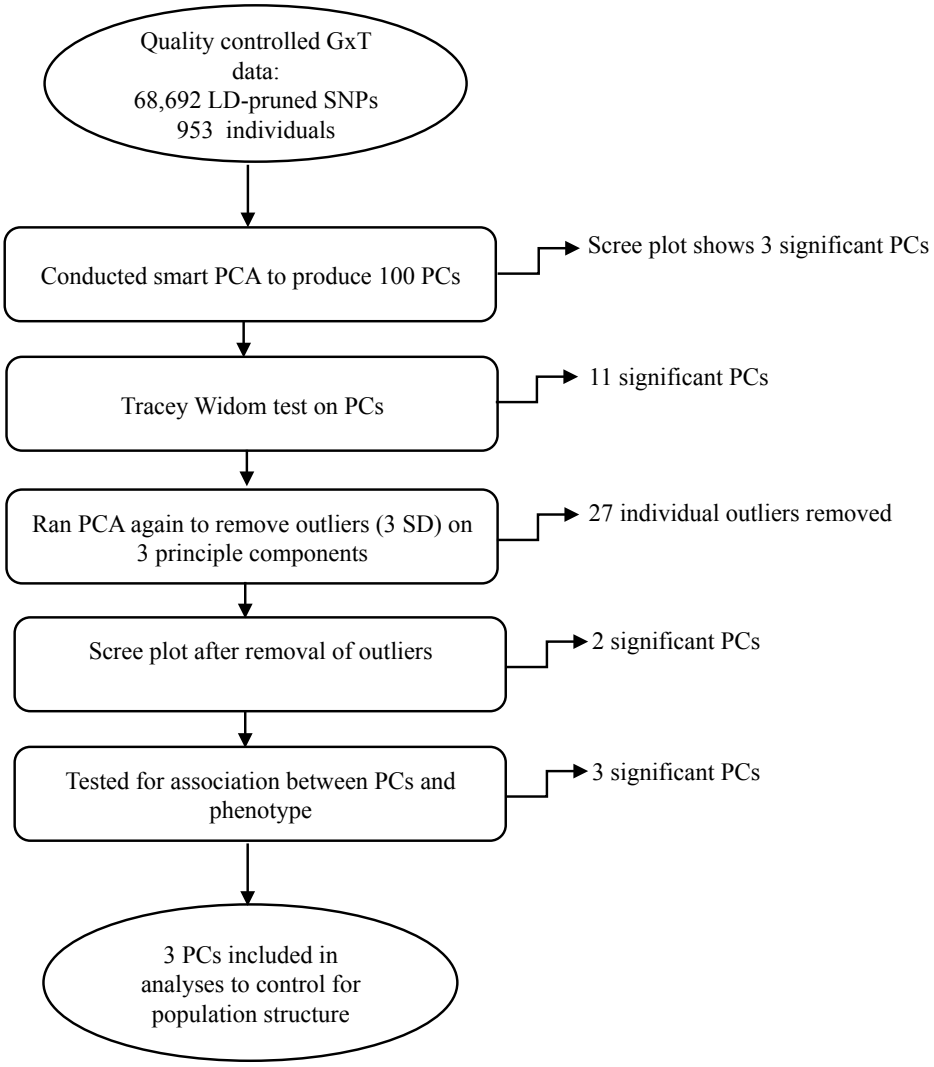


Figure 5.3b PCA analysis process (Study 3)

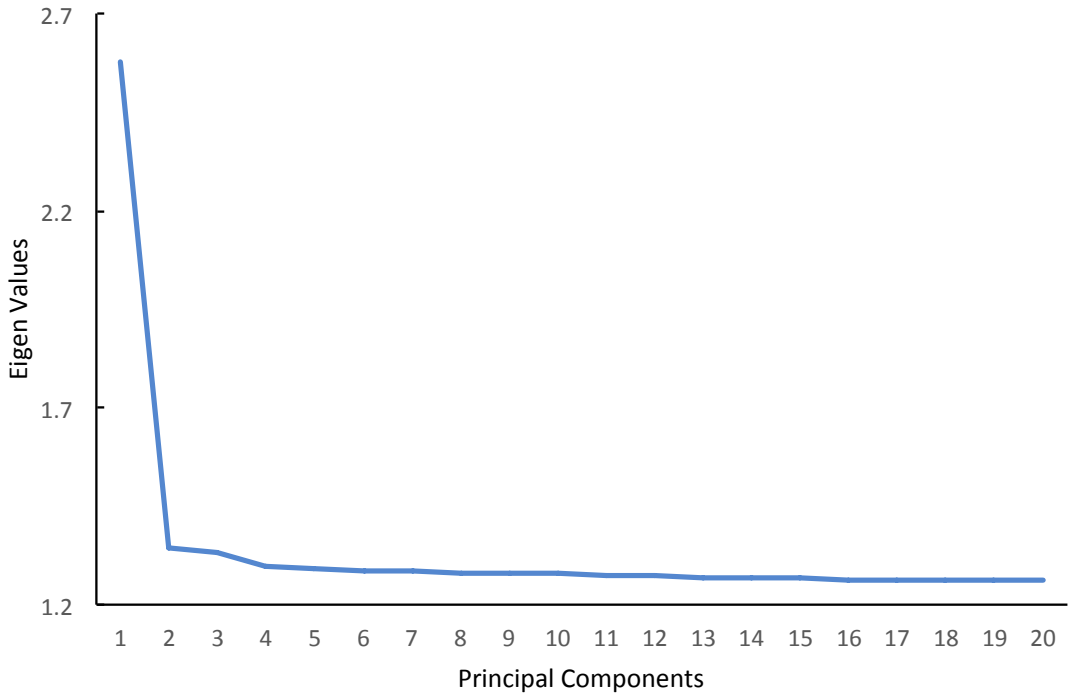


Figure 5.3c Scree plot of PCs after removal of individual outliers (Study 3)

5.2.3.2 Study 3: Data analysis

Analytical approach: The analyses were conducted to investigate the effects of the PGS of sensitivity on overall treatment response and differential response to the three treatment types.

The effect of PGS on overall treatment response was investigated by testing the effects of the PGS on change in severity of the primary anxiety diagnosis from baseline to post treatment and follow-up time points. Treatment specific effects were investigated by conducting analyses separately in those treated with individual CBT, group CBT and guided self-help and by testing PGS x treatment type interactions. Response to treatment was considered using data from the entire duration of the trial (post-treatment and 3 follow ups).

To make use of all available data on post treatment time points and to provide estimates in the presence of missing values, the effects of predictors on outcome were tested using linear mixed effect models fitted with full maximum likelihood. The following parameters were included as fixed effects: age (centred at mean), gender, baseline symptom severity (centred at the mean), anxiety diagnosis (in which SoAD, separation anxiety disorder [SAD], specific phobia [SP], and "other anxiety" disorders were each compared with generalized anxiety disorder [GAD]), treatment type (in which group-based and guided self-help CBT were each compared with individual-based CBT), linear and quadratic effects of time to account for the curvilinear slope of treatment outcome, 3 PCs to account for population stratification effects (centered at mean), and PGS of sensitivity (centred at mean). All models included the random effects of individual to account for correlations between repeated measures from the same participant, and higher-order random effect of trial to account for between-trial and between-site differences in outcome. For the GxE models, the interaction terms of PGS x treatment were included as the predictor, alongside other fixed and random effects. In all analyses, the coefficient values of variables predicting a more favourable response to treatment (i.e. greater reduction in severity) are negative, whereas variables predicting a less favourable response are positive.

Data Analysis Steps: First, analyses were conducted in order to examine whether genetic sensitivity biased treatment allocation or was over represented in specific diagnostic categories or correlated with symptom severity pre-treatment. To do this, ANOVAs were conducted, with PGS as the dependent variable and treatment type and

primary diagnosis category as the independent variable, to examine if there were differences in mean PGS score across the three treatment types or the 5 diagnostic categories at baseline. Pearson correlation was also conducted to examine the association between PGS and symptom severity at baseline. The effect of baseline symptom severity and age on treatment allocation was also examined using ANOVA. Chi-square analyses were conducted to see if allocation to treatment types were associated with diagnostic categories or gender.

Second, main effects of PGS on treatment response were examined, by including the PGS of sensitivity as a predictor of changes in symptom severity (4 time points) in a mixed linear regression model, alongside other fixed effect predictors which included baseline symptom severity (centered at the mean), treatment type (in which group-based and guided self-help CBT were each compared with individual-based CBT), age (centered at the mean), gender, the linear and quadratic effects of time, anxiety diagnosis, and 3 PCs.

Third, the effects of PGS in each treatment type was explored. This was done by using the same model as previous step, minus treatment, to predict treatment response in the three treatment groups (individual CBT, group CBT, guided self-help CBT).

Finally, an interaction term of PGS x treatment type (individual vs. group CBT; individual vs. guided self-help CBT; group vs. guided self-help CBT) was added to the model alongside variables from step 2 (baseline symptom severity, anxiety diagnosis category, treatment type, age, gender, linear and quadratic effects of time, polygenic score and PCs) to predict symptom severity post intervention. Significant interactions were then followed up using simple slopes analysis, with PGS at ± 2 *SD*, and environmental factor at 3 levels (low, medium, high).

5.2.4 Power analysis

G*Power 3.1 software (Faul et al., 2009) was used to determine the power to detect a range of expected effect sizes for the gene-environment interaction analyses in the current studies. Power analysis were conducted at two different p-value thresholds: nominal significance (alpha level of 0.05), and experiment-wide significance (alpha level of 0.001) which takes into account multiple testing of polygenic scores calculated at multiple thresholds (Euesden et al. (2015). The PGSxE interaction effects are expected to be small, based on other studies in the field using this approach. For example, Mullins et al. (2016), using a PGS of depression in interaction with childhood

trauma and SLEs in the same sample as Study 2, reported a significant but small odds ratio of .96 for the PGS x childhood trauma interaction, explaining 1.9% of the variance in depression. Similarly, using the same design and sample as the Study 3, Keers et al. (2016) reported significant interaction effects (PGS of differential susceptibility x treatment type), with the interaction terms explaining 1.6% to 5.7% of variance in treatment response. The same study found that a PGS x parenting interaction term explained .53% of the variance in children's emotional problems, an effect size comparable to other PGSxE studies, such as for major depression (Peyrot et al., 2014). The expected effect sizes for the interactions in the current studies are therefore expected to be small.

The results of the power analysis for Study 1, 2 and 3 are presented in **Figures 5.4a**, **5.4b** and **5.4c**, respectively. For Study 1, in a multiple linear regression model, the sample was adequately powered (70% power) to detect an effect that explained 0.21% of the variance at an alpha level of .05. However, at the lower alpha level of .001, the sample was only adequately powered to detect an effect that explained 0.51% of the variance. For Study 3, the sample was adequately powered (70% power) to detect an effect that explained 0.68% at the higher alpha of .05, however, at the lower alpha level of .001, the sample was only adequately powered to detect an effect that explained 1.6% of the variance. The repeated measures models used in the Study 1 and 3 is a more powerful approach than the ordinary linear regression models tested here, therefore these are more conservative estimate of power in these studies.

For Study 2, using a logistic regression model, there was over 70% power to detect an effect with an OR of .80 and lower, or 1.2 and higher, at an alpha level of .05. However, for the .001 alpha level, the power was reduced, with 70% power to detect an effect with an *OR* of .77 and lower or 1.3 and higher. The sample was insufficiently powered (< 10%) to detect smaller effect sizes (e.g. *OR*= .96) as reported in previous studies.

In summary, Study 1 and 3 were sufficiently powered to detect effects that explained as little as 0.5% of the variance and Study 2 was sufficiently powered to detect an effect with an OR smaller than .77 or larger than 1.3. Given that the power analysis showed that all studies would be insufficiently powered to detect smaller effect sizes, it was decided to report all results of nominal significance ($p < .05$), as well as any experiment-wide significant results with $p < .001$, which takes into account multiple testing of polygenic scores calculated at multiple thresholds (Euesden et al., 2015).

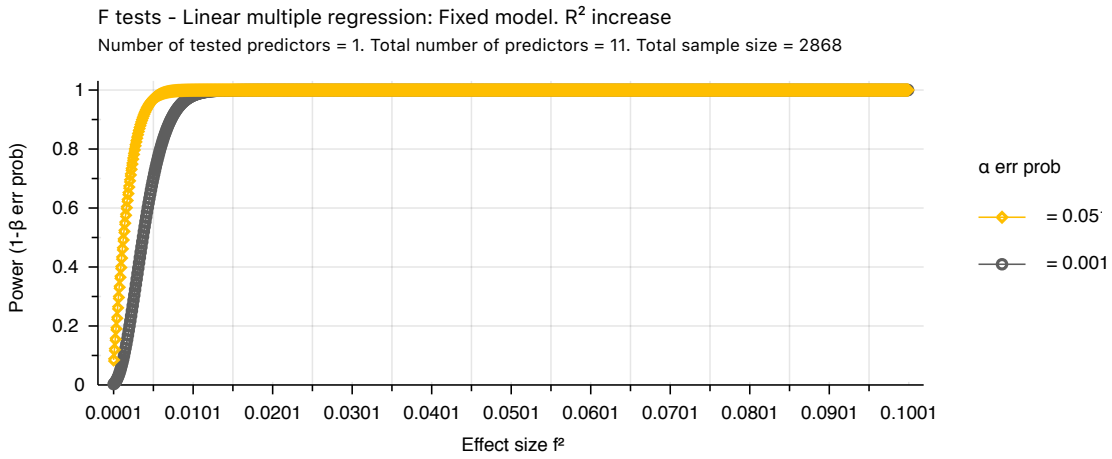


Figure 5.4a Power analysis of Study 1

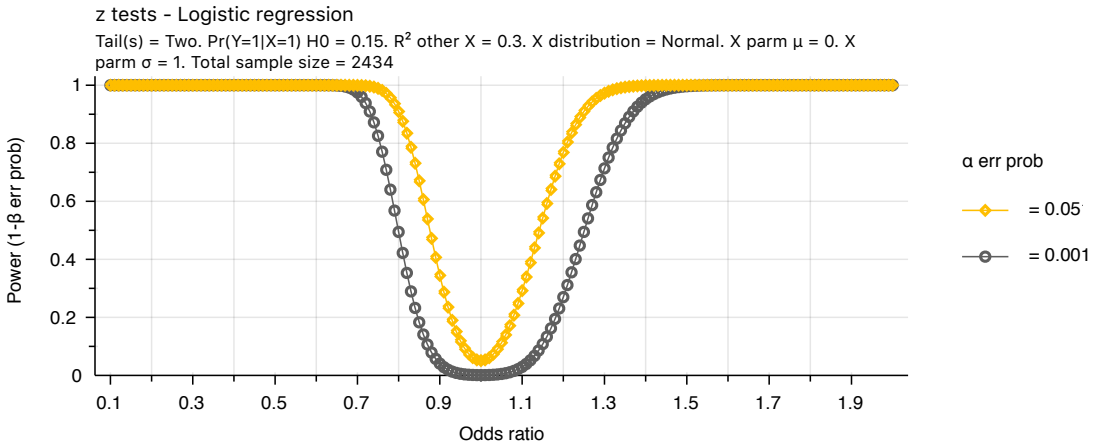


Figure 5.4b Power analysis of Study 2

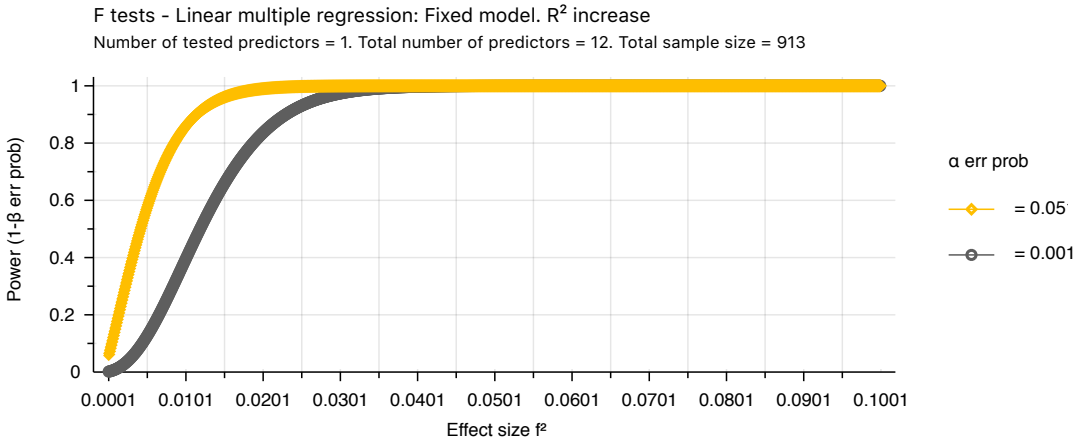


Figure 5.4c Power analysis of Study 3

5.3 Results

5.3.1 Study 1: Results

5.3.1.1 Study 1: Descriptive statistics

Descriptive statistics of the sample, including sample size at each age, and mean scores of environmental quality in childhood and adulthood, psychological distress are presented in **Table 5.1a.** Bivariate correlations between all study variables are presented in **Table 5.1b.** There were significant positive correlations between measures of quality of environment across lifespan (r= .18 to .53), such that higher childhood psychosocial environmental quality was associated with higher adulthood psychosocial environmental quality, with temporally closer time points showing larger correlations.

Psychological distress scores were also positively correlated across childhood time points (r= .10 to .18), and adulthood time points (r= .43 to .45). The correlations between childhood and adulthood psychological distress were also significant, though to a lesser degree (r= .02 to .06).

Overall, higher scores on environmental quality were correlated with lower risk of psychological distress. Female gender was associated with higher levels of psychological distress in adulthood, but lower levels of distress in childhood. Males showed the opposite effect, whereby they had higher scores on psychological distress in childhood, but lower scores in adulthood. Gender was also associated with environmental quality in adulthood, whereby there was a significant positive correlation between higher environmental quality at ages 33, 42, and 50 and being male.

Table 5.1a Descriptive statistics of the sample (Study 1)

	Sample Size			Mean score (*SD*)	
	Environmental quality	Psychological distress	Gender (% female)	Environmental quality	Psychological distress
Age 7	1483	2626	48.82	.06 (0.025)	-.09 (.02)
Age 11	1467	2499	48.18	.06 (0.02)	-.08 (.02)
Age 16	1336	.	48.13	.04 (0.03)	.
Age 23	497	2475	48.97	.15 (0.04)	-.06 (.02)
Age 33	2107	2579	49.44	.08 (0.02)	-.07 (.02)
Age 42	2337	2765	48.14	.07 (0.02)	-.06 (.02)
Age 50	2185	2535	48.64	.05 (0.02)	-.05 (.02)

Genetic data was available for all individuals; scores for all variables are standardised, with higher scores indicating higher levels of environmental quality and psychological distress; Empty cell indicate no data was available for the variable at the specific age.

Table 5.1b Bivariate correlations between study variables (Study 1)

		1	2	3	4	5	6	7	8	9	10	11	12	13
1	**ENV7**													
2	**ENV11**	.53*												
3	**ENV16**	.36*	.36*											
4	**ENV23**	.23*	.17*	.08										
5	**ENV33**	.23*	.29*	.24*	.41*									
6	**ENV42**	.18*	.20*	.21*	.33*	.55*								
7	**ENV50**	.19*	.21*	.24*	.34*	.47*	.64*							
8	**PD7**	-.21*	-.20*	-.18*	-.15*	-.15*	-.12*	-.12*						
9	**PD11**	-.16*	-.26*	-.17*	-.08	-.20*	-.14*	-.15*	.18*					
10	**PD33**	-.12*	-.13*	-.20*	-.17*	-.20*	-.18*	-.16*	.02	.10*				
11	**PD42**	-.02	-.10*	-.13*	-.08	-.11*	-.09*	-.10*	.06*	.05*	.45*			
12	**PD50**	-.03	-.09*	-.10*	-.18*	-.13*	-.10*	-.10*	.02	.04*	.43*	.56*		
13	**Sex**	-.01	.02	-.02	.06	-.08*	-.09*	-.07*	-.11*	-.07*	.28*	.18*	.17*	
14	**PGS1**	-.03	.00	-.02	.05	.02	.04	.00	-.01	-.01	-.05	-.03	-.04	-.04
15	**PGS2**	.00	-.01	-.04	.06	.01	.01	-.01	-.02	-.02	-.03	-.03	-.01	-.02
16	**PGS3**	-.04	.01	-.01	.00	.03	-.01	-.03	.00	.00	-.02	-.04	-.02	.00
17	**PGS4**	-.03	.01	-.02	.00	.02	-.02	-.03	.00	-.01	-.01	-.03	.00	.01
18	**PGS5**	-.02	.02	-.01	.01	.02	-.02	-.03	.00	-.02	-.01	-.02	.00	.01
19	**PGS6**	-.02	.03	-.01	.01	.02	-.01	-.03	-.01	-.02	-.01	-.02	.00	.02
20	**PGS7**	-.02	.01	.00	.00	.02	-.01	-.03	.00	-.02	-.02	-.02	.01	.02
21	**PGS8**	-.02	.02	.00	.00	.02	-.01	-.03	-.01	-.02	-.01	-.02	.01	.02
22	**PGS9**	-.02	.02	.00	.01	.02	-.01	-.02	-.01	-.02	-.02	-.02	.01	.01

ENV=Environmental quality at each age; PD= Psychological distress at each age; PGS=Polygenic score of environmental sensitivity at different thresholds; PGS=polygenic score at different thresholds; * $p < .05$

5.3.1.2 Study 1: Main effects of PGS and childhood environmental quality on psychological distress in adulthood

There was a main effect of psychosocial environment at all ages during childhood (7, 11 and 16) as well as concurrent adulthood environment on adulthood psychological distress. The associations were in the expected direction, with higher quality childhood or adulthood environment associated with lower psychological distress in adulthood. There were significant effects of overall childhood environment and concurrent adult environment on psychological distress (β= -.13, p < 4E-14 and β=-.07, p < 6E-10, respectively). There were no significant effects of polygenic scores of sensitivity on psychological distress, except for a small protective effect of PGS1 on psychological distress (β= -.03, p= .02). Full results are presented in **Table 5.2**.

Table 5.2 Main effects of PGS and environmental quality on psychological distress in adulthood (Study 1)

	β	CI	*p*
Environment age 7	**-.07**	**-.11, -.03**	**3.00E-04**
Environment age 11	**-.12**	**-.15, -.08**	**2.00E-09**
Environment age 16	**-.14**	**-.17, -.10**	**8.00E-13**
Overall childhood environment	**-.13**	**-.16, -.09**	**4.00E-14**
Adult environment	**-.07**	**-.09, -.05**	**6.00E-10**
PGS1	**-.03**	**-.06, -.00**	**.02**
PGS2	-.02	-.05, .01	.11
PGS3	-.02	-.05, .00	.11
PGS4	-.02	-.04, .01	.26
PGS5	-.01	-.04, .02	.42
PGS6	-.01	-.04, .02	.46
PGS7	-.01	-.04, .01	.33
PGS8	-.01	-.04, .02	.40
PGS9	-.01	-.04, .01	.31

PGS= Polygenic Score; β= standardized beta coefficient of the variable from the regression model; CI=95% Confidence interval; p =p-value of the beta Regression model for environmental factors: decades, sex, and E factor as fixed effects, plus individual as random effect; Regression model for PGS: decades, sex, PGS, and PCs 1 to 3 as fixed effects, plus individual as random effect

5.3.1.3 Study 1: PGS x environment interaction effects on psychological distress in adulthood

The results of the GxE interaction analyses for PGS of sensitivity and environmental quality at ages 7, 11, 16, overall childhood, and concurrent adult environment are presented in **Table 5.3**. There was a small, but statistically significant GxE effect for environmental quality at age 7 and PGS 4 (β= .04, $p < .05$). Though none of the other interactions were found to be significant, they were all in the same direction. Simple slopes analysis of the significant interaction show that the direction of effect was contrary to the study hypothesis. As shown in **Figure 5.5**, higher genetic sensitivity was associated with decreased risk of adulthood psychological distress in the context of low quality environment at age 7, and higher risk of distress in the context of high quality childhood environment.

Table 5.3 PGS x environmental quality interaction in predicting psychological distress in adulthood (Study1)

	Environmental quality across ages														
	Age 7			Age 11			Age 16			Overall childhood			Concurrent adulthood		
	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*
PGS1	.03	-.01, .07	.18	.01	-.03, .05	.60	.00	-.04, .04	.96	.01	-.03, .04	.71	.00	-.02, .02	.98
PGS2	.04	-.00, .08	.07	.01	-.03, .05	.54	.02	-.01, .06	.22	.01	-.02, .05	.39	.02	-.01, .04	.21
PGS3	.03	-.01, .06	.20	.01	-.03, .05	.60	.02	-.02, .06	.26	.01	-.02, .05	.51	-.01	-.03, .02	.52
PGS4	**.04**	**.00, .08**	**.04**	.02	-.02, .06	.42	.02	-.02, .06	.28	.02	-.01, .06	.18	.00	-.03, .02	.68
PGS5	.04	-.00, .08	.07	.02	-.02, .06	.37	.02	-.02, .06	.25	.03	-.01, .06	.12	.00	-.02, .03	.82
PGS6	.03	-.01, .07	.09	.01	-.03, .05	.51	.02	-.02, .06	.30	.03	-.01, .06	.15	.01	-.02, .03	.50
PGS7	.04	-.01, .08	.09	.01	-.03, .05	.54	.02	-.02, .06	.36	.02	-.01, .06	.22	.01	-.01, .03	.43
PGS8	.03	-.01, .07	.12	.01	-.03, .05	.75	.01	-.02, .05	.47	.02	-.02, .05	.37	.01	-.01, .03	.41
PGS9	.03	-.01, .07	.11	.01	-.03, .05	.73	.01	-.02, .05	.46	.02	-.02, .05	.32	.01	-.01, .03	.46

PGS= Polygenic Score; β = standardized beta coefficient of the variable from the regression model; CI=95% Confidence interval; *p* =*p*-value of the beta; Regression models for childhood environments include: fixed effects (PGS x childhood environment interaction term, childhood environment, PGS, adult environment, 3 PCs, sex, decades) and random effect (individual); Regression model for concurrent adult environment includes: fixed effects (PGS x adult environment interaction term, adult environment, PGS, overall childhood environment, PCs 1 to 3, sex, decades) and random effect (individual)

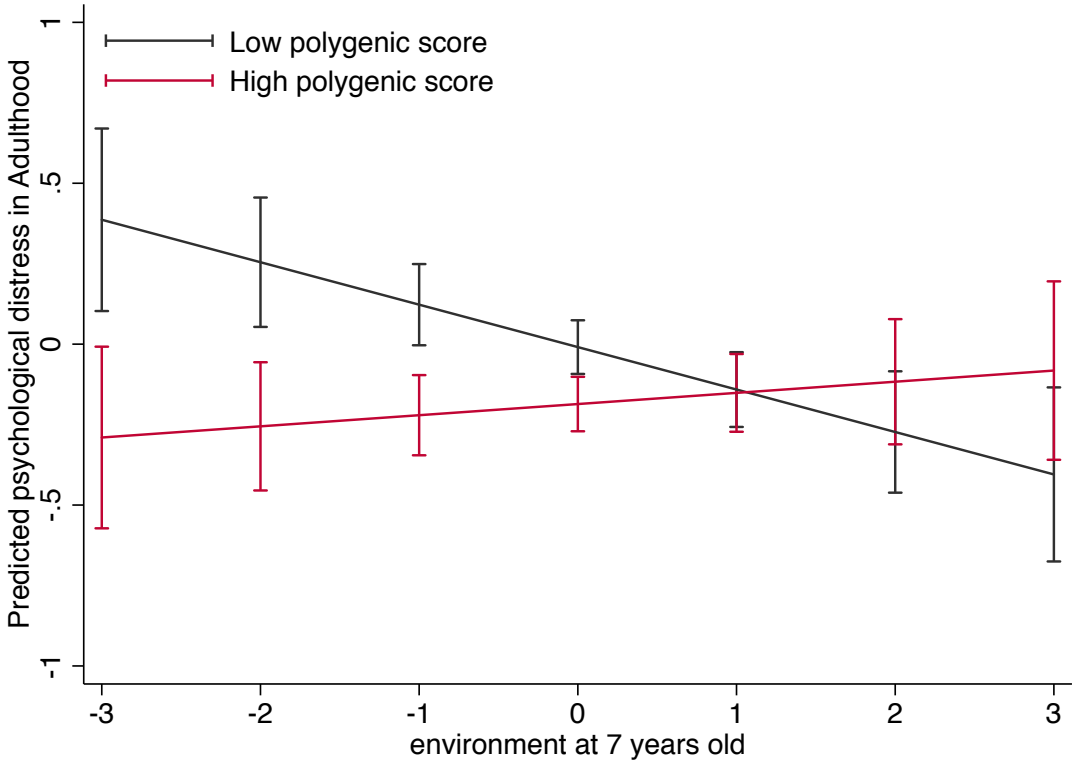


Figure 5.5 PGS x childhood environmental quality predicting psychological distress in adulthood (Study 1)

Post hoc analyse were conducted to explore whether the gene-environment interaction findings differed according to the proximity of the environmental exposure to the outcome. In order to allow for the maximum time between environment and outcome measures these analyses focused on the effects of childhood environment at age 7. A single linear mixed model was fitted with psychological distress at all available ages (7, 11, 23, 33, 42, and 50) as the outcome. Predictors included the fixed effects of psychosocial environment (at age 7), PGS and time and the two and three-way interaction terms between each of these variables (i.e. PGS x time, PGS x environment, time x environment, PGS x environment x time). The results of this model are presented in **Table 5.4.** A small (β= .001 and .002) but significant 3-way interaction was detected for several PGSs (PGS 2, 3, 4 and 7) indicating that PGS by environment interactions differed as a function of time.

Table 5.4 Results of three-way interaction model with PGS x environment quality at age 7 x time predicting psychological distress across life span (Study 1)

	PGS		Time		Env age 7		PGS x Env age 7		PGS x Time		PGS x Env age 7 x Time	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
PGS1	-.01	.79	.001	.18	**-.21**	**<1E-18**	-.01	.65	-.00	.09	.00	.14
PGS2	.01	.60	.001	.22	**-.21**	**<1E-18**	**-.04**	**.04**	**-.001**	**.02**	**.002**	**4E-04**
PGS3	-.01	.59	.001	.18	**-.21**	**<1E-18**	-.03	.14	-.00	.29	**.001**	**0.02**
PGS4	-.02	.38	.001	.17	**-.21**	**<1E-18**	-.04	.10	.00	.57	**.002**	**4E-03**
PGS5	-.03	.11	.001	.19	**-.21**	**<1E-18**	-.02	.49	.00	.92	.001	.06
PGS6	-.04	.06	.001	.18	**-.21**	**<1E-18**	-.02	.45	.00	.51	.001	.08
PGS7	-.04	.07	.001	.18	**-.21**	**<1E-18**	-.02	.42	.00	.58	**.001**	**.05**
PGS8	-.04	.08	.001	.19	**-.21**	**<1E-18**	-.02	.50	.00	.64	.001	.08
PGS9	-.04	.06	.001	.19	**-.21**	**<1E-18**	-.02	.47	.00	.69	.001	.07

PGS= Polygenic score; Env= psychosocial environmental quality; β= standardized beta coefficient of the variable from the regression model; Mixed effects linear regression with psychological distress at ages 7, 11, 23, 33, 42, and 50 as predictor, and fixed effects of environmental quality at age 7, PGS, time, PGS x time x environment at age 7 interaction term, PGS x time interaction term, PGS x environment at age 7 interaction term, time x environment at age 7 interaction term, sex and 3 PCs, and individual as random effect

In order to probe these three-way interactions on psychological distress, the analyses were repeated in a series of linear regression models fitted separately for each time point. **Table 5.5** presents the findings from the age 7 and age 11 time points (there was no data on psychological distress at age 16). Although the interactions were not statistically significant, except for a marginal effect for PGS4 at age 7 (β= -.04, p = .07), findings were in the opposite direction to those observed at the adult time points. That is, high genetic sensitivity was associated with greater psychological distress in poor-quality environments but was protective in high quality environments.

Figure 5.6, shows the PGS4 x environment at age 7 on psychological distress at each time point from childhood to adulthood. They show that, in line with the direction of effects indicated by the 3-way interaction, the effects of high genetic sensitivity gradually reverse over time. That is, high genetic sensitivity is associated with higher distress in a poor-quality environment in childhood, but lower distress later on in adulthood. The slopes remain relatively stable for low genetically sensitive individuals across life.

Table 5.5 Interaction effects of PGS x environmental quality at age 7 and 11 in predicting psychological distress at ages 7 and 11 (Study 1)

	Environmental Factor			**PGS of Sensitivity**			**PGS x E Interaction**		
	β	CI	*p*	β	CI	*p*	β	CI	*p*
Environmental Quality at age 7									
PGS1	**-.21**	**(-.26, -.16)**	**2E-17**	-.01	(-.06, .03)	.54	.01	(-.04, 0.05)	.73
PGS2	**-.21**	**(-.26, -.16)**	**1E-17**	.02	(-.03, .06)	.49	-.03	(-.08, 0.01)	.17
PGS3	**-.21**	**(-.26, -.16)**	**2E-17**	-.01	(-.05, .04)	.76	-.03	(-.08, .01)	.16
PGS4	**-.21**	**(-.26, -.16)**	**2E-17**	.00	(-.05, .04)	.88	**-.04**	**(-.09, .00)**	**.07**
PGS5	**-.21**	**(-.26, -.16)**	**2E-17**	-.01	(-.06, .04)	.65	-.03	(-.08, .02)	.20
PGS6	**-.21**	**(-.26, -.16)**	**2E-17**	-.02	(-.06, .03)	.43	-.03	(-.08, .02)	.29
PGS7	**-.21**	**(-.26, -.16)**	**2E-17**	-.01	(-.06, .04)	.69	-.03	(-.08, .02)	.18
PGS8	**-.21**	**(-.26, -.16)**	**2E-17**	-.01	(-.06, .04)	.68	-.03	(-.08, .02)	.21
PGS9	**-.21**	**(-.26, -.16)**	**2E-17**	-.01	(-.06, .03)	.61	-.03	(-.08, .02)	.20
Environmental Quality at age 11									
PGS1	**-.25**	**(-.30, -.20)**	**<1E-18**	-.02	(-.06, .03)	.45	-.01	(-.06, .03)	.57
PGS2	**-.25**	**(-.30, -.20)**	**<1E-18**	-.01	(-.06, .03)	.55	-.02	(-.07, .02)	.29
PGS3	**-.25**	**(-.30, -.20)**	**<1E-18**	-.01	(-.05, .04)	.73	-.04	(-.08, .01)	.11
PGS4	**-.25**	**(-.30, -.20)**	**<1E-18**	.00	(-.05, .04)	.94	-.03	(-.08, .02)	.22
PGS5	**-.25**	**(-.30, -.20)**	**<1E-18**	.00	(-.05, .04)	.86	-.03	(-.07, .02)	.28
PGS6	**-.25**	**(-.30, -.20)**	**<1E-18**	.00	(-.04, .04)	.96	-.02	(-.07, .02)	.30
PGS7	**-.25**	**(-.30, -.20)**	**<1E-18**	.00	(-.05, .04)	.86	-.02	(-.07, .02)	.32
PGS8	**-.25**	**(-.30, -.20)**	**<1E-18**	.00	(-.05, .04)	.94	-.02	(-.07, .03)	.39
PGS9	**-.25**	**(-.30, -.20)**	**<1E-18**	-.01	(-.05, .04)	.74	-.02	(-.06, .03)	.49

PGS= Polygenic score; β= standardized beta coefficient from the regression model; CI=95% confidence interval; *p* =*p*-value; significant interactions are in bold; Linear regression models included psychological distress (at age 7 or 11) as the outcome, and environmental quality (at age 7 or 11), PGS, PGS x Environment interaction term, 3PCs and sex as predictors.

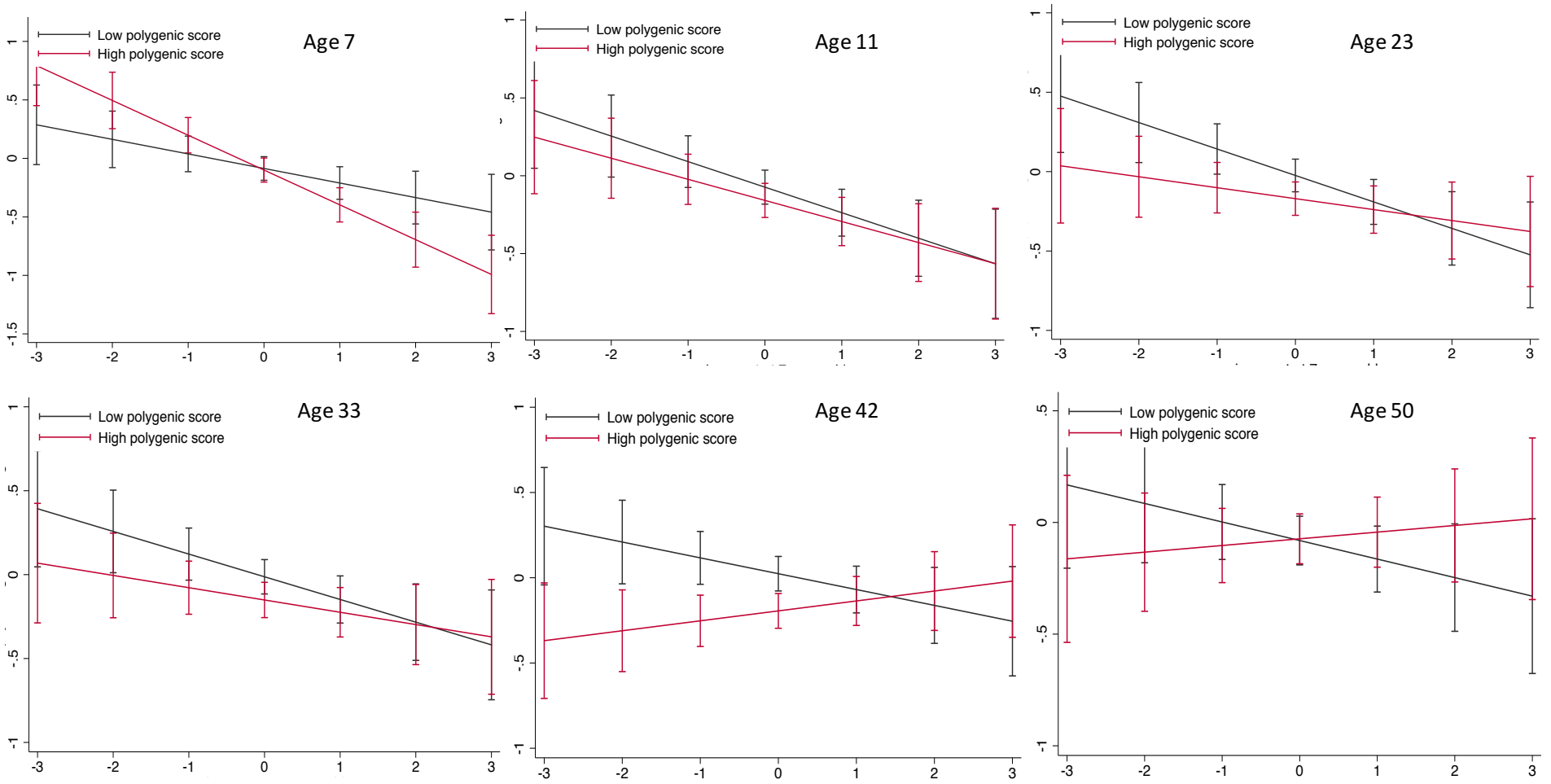


Figure 5.6 Simple slopes analysis of the effect of environmental quality at 7 predicting psychological distress across life span (Study 1)
The x-axis represent environmental quality at age 7, and the y-axis represent psychological distress (z-scores) at different ages, indicated at the top of each chart.

5.3.1.4 Study 1: Gene-environment correlation

The results of the linear regression analyses, with each environmental variable as the outcome and PGS as the predictor and sex and 3 PCs as covariates are presented in **Table 5.6**. There were no significant correlations between any of the examined PGS and environmental factors.

Table 5.6 Gene-environment correlation analyses (Study 1)

	Childhood environmental quality							
	Age 7		Age 11		Age 16		Overall childhood environment	
	β	*p*	β	*p*	β	*p*	β	*p*
PGS1	-.03	.27	-.01	.82	-.01	.61	-.02	.38
PGS2	.00	.91	-.01	.77	-.03	.18	-.02	.16
PGS3	-.04	.14	.01	.78	-.01	.70	-.02	.18
PGS4	-.03	.23	.01	.81	-.02	.47	-.02	.24
PGS5	-.02	.40	.02	.37	-.01	.76	-.01	.78
PGS6	-.02	.37	.02	.32	-.01	.68	.00	.80
PGS7	-.02	.41	.01	.60	.00	.98	.00	.83
PGS8	-.02	.49	.02	.50	.00	.94	.00	.93
PGS9	-.02	0.48	.02	.40	.00	.91	.00	.97
	Adulthood environmental quality							
	Age 23		Age 33		Age 42		Age 50	
	β	*p*	β	*p*	β	*p*	β	*p*
PGS1	.04	.32	.01	.48	.04	.06	.00	.92
PGS2	.06	.18	.01	.67	.02	.42	-.01	.69
PGS3	.00	.99	.03	.11	.00	.91	-.03	.19
PGS4	-.01	.90	.02	.45	-.01	.44	-.03	.17
PGS5	.01	.89	.02	.42	-.02	.42	-.03	.13
PGS6	.01	.90	.02	.42	-.01	.70	-.03	.21
PGS7	.00	.99	.02	.44	-.01	.68	-.03	.19
PGS8	.00	.98	.02	.40	.00	.94	-.02	.25
PGS9	.00	.92	.02	.40	.00	.90	-.02	.29

PGS= Polygenic Score; β= standardized beta coefficient of the variable from the regression model; Linear regression model included environmental variable as the outcome, and PGS as the predictor with sex and 3 PCs as the covariates

5.3.2 Study 2: Results

5.3.2.1 Study 2: Descriptive statistics

Descriptive statistics of the sample, including sample size, childhood traumas, stressful life events (SLEs), and number of cases/controls are presented in **Table 5.7a.** Cases included a significantly larger proportion of females (X^2= 51.89, p< .001) and also experienced higher levels of SLEs (X^2= 16.77, p< .001) than controls.

Bivariate correlations between all study variables are presented in **Table 5.7b.** The results showed all maltreatment types to be significantly and positively correlated (r= .17 to .63), and childhood maltreatment was also correlated positively and significantly with SLEs (r= .16 to .23). Female gender was associated with higher levels of sexual and emotional abuse (r=.14 and .12, respectively). Polygenic scores of sensitivity were not significantly correlated with any of the other variables.

Table 5.7a Descriptive statistics of the sample (Study 2)

	Cases	**Controls**
Sample * *n*	1530	904
Age	30.07 (.50)	42.64 (.53)
Sex, *n*		
Male	447	394
Female	1083	510
Stressful life events, *n*		
Low	388	480
Moderate	479	289
High	663	135
Sexual abuse	7.05 (.30)	5.48 (.13)
Physical abuse	6.76 (.21)	5.61 (.09)
Emotional abuse	11.24 (.38)	6.82 (.18)
Physical neglect	8.09 (.23)	6.15 (.13)
Emotional neglect	13.15 (.38)	8.70 (.22)
Overall maltreatment, *n*		
Low/None	94	225
Moderate	84	35
High	52	6

The statistics given are mean (*SD*) unless otherwise specified; * the sample with childhood maltreatment data was *N*=496, with 230 cases and 266 controls

Table 5.7b Bivariate correlations between study variables (Study 2)

	Sex	Age	Dep	SLEs	SA	PA	EA	PN	EN	OM
Age	-.10*									
Depression	.15*	-.27*								
Stressful life events	.08*	-.11*	.33*							
Sexual abuse	.14*	-.15*	.22*	.16*						
Physical abuse	.02	-.09*	.23*	.17*	.26*					
Emotional abuse	.12*	-.21*	.45*	.32*	.37*	.55*				
Physical neglect	-.01	-.09*	.32*	.22*	.32*	.31*	.47*			
Emotional neglect	-.01	-.14*	.42*	.23*	.28*	.34*	.59*	.63*		
Overall maltreatment	.05	-.23*	.46*	.31*	.51*	.57*	.79*	.70*	.73*	
PGS1	-.02	-.03	.01	.01	.04	.06	.06	.08	.08	.08
PGS2	-.02	.00	.02	-.02	.02	.02	.07	.07	.04	.06
PGS3	-.01	-.01	.02	.00	.03	.05	.06	.04	.06	.06
PGS4	-.01	.00	.02	.01	.04	-.01	.05	.00	.07	.05
PGS5	.00	-.02	.03	-.01	.05	-.02	.04	.01	.04	.03
PGS6	.01	-.01	.02	-.01	.06	-.01	.06	.02	.06	.04
PGS7	.01	-.02	.02	-.01	.05	.01	.06	.02	.06	.04
PGS8	.00	-.02	.02	-.01	.06	.01	.07	.02	.07	.05
PGS9	.00	-.02	.02	-.01	.07	.01	.08	.03	.07	.06

* *p* -value < .05; Dep= Depression; SLEs= Stressful life events; SA= Sexual abuse; PA=Physical abuse; EA=emotional abuse; P*N*=Physical neglect; EN=emotional neglect; OM=Overall maltreatment; PGS=Polygenic score

5.3.2.2 Study 2: Main effects of SLEs and maltreatment and PGS of environmental sensitivity on depression

The results of analysis examining the effects of PGS and environmental factors on depression are presented in **Table 5.8**. The results showed a significant main effect of SLEs on depression, such that higher/more severe levels of SLE's were associated with two-fold increase in risk of depression (*OR*= 2.32, $p < .001$). There were also significant main effects of childhood maltreatment (overall and subscales) such that any type of childhood maltreatment increased the risk of having depression, with the largest effect seen for physical neglect and abuse (*OR*= 1.28, $p < .001$). There was a significant effect of overall childhood maltreatment, (*OR* = 4.46, $p < .01$), indicating the risk of depression was over four times greater for those who had experienced maltreatment compared to those who had not. There was a general trend towards higher risk of depression with increased genetic sensitivity, though the associations were not statistically significant.

Table 5.8 Main effects of PGS, stressful life events, and childhood maltreatment on depression (Study 2)

	OR	CI	*p*
Stressful life events	**2.32**	**2.07, 2.60**	**3E-09**
Sexual abuse	**1.15**	**1.05, 1.25**	**2E-03**
Physical abuse	**1.28**	**1.15, 1.43**	**1E-05**
Emotional abuse	**1.23**	**1.16, 1.30**	**4E-12**
Physical neglect	**1.28**	**1.18, 1.39**	**3E-09**
Emotional neglect	**1.20**	**1.15, 1.27**	**2E-13**
Overall childhood maltreatment	**4.46**	**3.03, 6.56**	**4E-14**
PGS1	1.10	.90, 1.35	.36
PGS2	1.09	.90, 1.33	.38
PGS3	1.14	.92, 1.40	.22
PGS4	1.12	.91, 1.38	.28
PGS5	1.07	.87, 1.31	.52
PGS6	1.09	.90, 1.33	.38
PGS7	1.10	.90, 1.34	.37
PGS8	1.09	.90, 1.33	.41
PGS9	1.13	.92, 1.38	.24

PGS= Polygenic Score; OR= Odds ratio form logistic regression model; CI=95% Confidence interval; Logistic regression models included depression case/control status as the outcome, and the environmental factor or PGS with age, sex and 3 PCs as covariates; $p < .05$ are in bold.

5.3.2.3 Study 2: PGS x environment interaction effects on depression

In order to examine whether the PGS moderated the effects of the environment on major depression, the environmental factor (SLE or maltreatment), PGS and an environment x PGS interaction term were included as predictors in logistic regression model with case/control status as the outcome. Analyses were conducted separately for each environmental variable. Age, sex and 3 PCs were included as covariates in all analyses.

The results of these analyses are presented in **Table 5.9**. Genetic sensitivity x recent SLE's interactions were not statistically significant, but were in the expected direction. High sensitivity was associated with a slight increased risk of depression (*OR*= 1.06, *p*= .32) in the presence of recent SLEs.

Significant GxE effects were identified for overall childhood maltreatment (*OR*= .66, *p*= .04), and sexual abuse (*OR*= .89, *p*= .02). The interaction term explained .06% and .08% of the variance in depression, respectively. However, the simple slopes analysis, as presented in **Figure 5.7a**, show that this pattern of interaction was contrary to expectations. That is, in the absence of/low levels of childhood maltreatment, high sensitivity increased risk of depression in adulthood, but in the presence of severe maltreatment, genetic sensitivity acted as a protective factor. Conversely, low genetic sensitivity was associated with a low risk of depression in the absence of childhood maltreatment and increased depression risk in the context of severe maltreatment. A similar interaction pattern was found for the significant interaction between sexual abuse and depression risk (**Figure 5.7b**). Although not statistically significant, interactions across all types of maltreatment showed a similar pattern, except for the interaction with physical neglect that showed a small (*OR*= 1.02) opposite effect by increasing the risk for depression (**Table 5.9**).

Table 5.9 Interaction effects of SLEs and childhood maltreatment with PGS in predicting depression (Study 2)

	SLEs		Overall maltreatment		Sexual abuse		Physical abuse		Emotional abuse		Physical neglect		Emotional neglect	
	OR (CI)	*p*	OR (CI)	*p*	OR (CI)	*p*	OR (CI)	*p*	OR (CI)	*p*	OR (CI)	*p*	OR (CI)	*p*
PGS1	1.03 (.92, 1.15)	0.63	**0.66 (.44, .99)**	**0.04**	**0.89** (.81, .98)	**0.02**	0.89 (.77, 1.02)	0.10	0.98 (.92, 1.05)	0.60	0.97 (.88, 1.06)	0.49	0.95 (.90, 1.00)	0.06
PGS2	1.02 (.91, 1.14)	0.76	0.96 (.67, 1.38)	0.83	0.97 (.89, 1.06)	0.52	0.97 (.86, 1.08)	0.54	1.01 (.95, 1.07)	0.83	1.02 (.95, 1.11)	0.56	0.99 (.95, 1.04)	0.70
PGS3	1.06 (.94, 1.19)	0.32	0.89 (.61, 1.28)	0.52	0.97 (.89, 1.06)	0.46	0.97 (.89, 1.05)	0.42	0.99 (.93, 1.06)	0.83	1.07 (.98, 1.17)	0.14	0.98 (.94, 1.03)	0.52
PGS4	1.05 (.94, 1.18)	0.40	0.78 (.54, 1.14)	0.20	0.96 (.89, 1.03)	0.24	0.93 (.85, 1.02)	0.11	0.97 (.91, 1.03)	0.34	1.07 (.98, 1.16)	0.14	0.98 (.93, 1.03)	0.36
PGS5	1.05 (.94, 1.18)	0.37	0.77 (.54, 1.10)	0.15	0.95 (.87, 1.03)	0.22	0.94 (.86, 1.03)	0.18	0.98 (.93, 1.04)	0.58	1.04 (.97, 1.12)	0.29	0.97 (.93, 1.02)	0.28
PGS6	1.05 (.93, 1.18)	0.43	0.77 (.54, 1.12)	0.17	0.95 (.88, 1.04)	0.27	0.94 (.86, 1.03)	0.17	0.99 (.93, 1.05)	0.65	1.02 (.94, 1.10)	0.70	0.98 (.93, 1.03)	0.36
PGS7	1.04 (.93, 1.17)	0.49	0.8 (.54, 1.17)	0.24	0.96 (.88, 1.04)	0.31	0.95 (.86, 1.04)	0.28	0.99 (.93, 1.06)	0.83	1.02 (.94, 1.11)	0.64	0.98 (.93, 1.03)	0.48
PGS8	1.04 (.93, 1.16)	0.53	0.79 (.53, 1.16)	0.23	0.95 (.87, 1.03)	0.23	0.95 (.86, 1.04)	0.26	0.99 (.93, 1.05)	0.79	1.03 (.95, 1.12)	0.51	0.98 (.93, 1.03)	0.40
PGS9	1.05 (.94, 1.18)	0.41	0.8 (.54, 1.18)	0.25	0.96 (.88, 1.04)	0.31	0.94 (.86, 1.04)	0.22	0.99 (.93, 1.06)	0.80	1.03 (.95, 1.12)	0.48	0.98 (.93, 1.03)	0.45

PGS= Polygenic score; OR= Odds ratio form logistic regression model; CI=95% Confidence interval; Logistic regression models included depression case/control status as the outcome, and the environmental factor, PGS, the environment x PGS interaction term, age, sex and 3 PCs as predictors; $p < .05$ are in bold

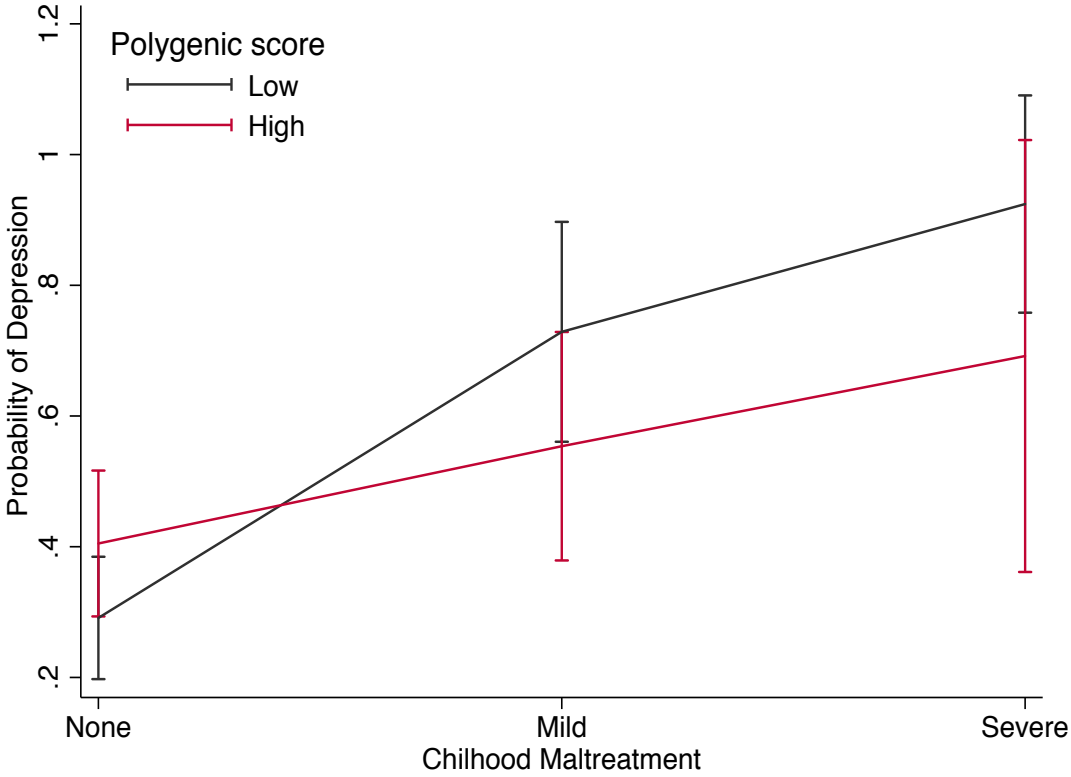


Figure 5.7a Simple slopes analysis of the interaction between PGS x overall childhood maltreatment in probability of depression in adulthood

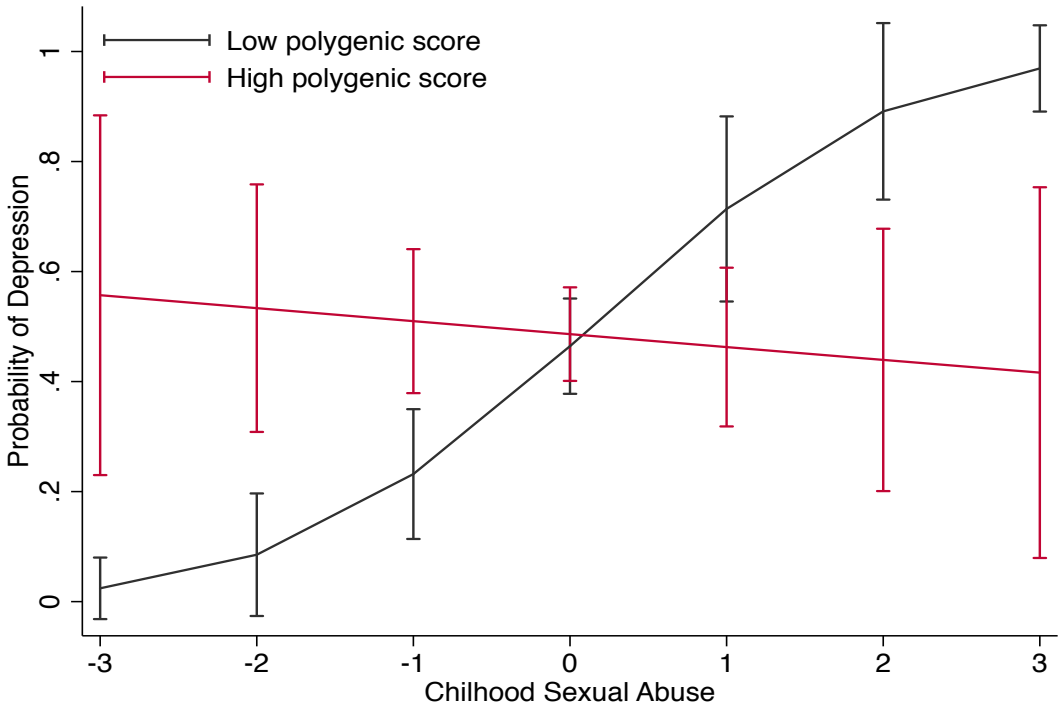


Figure 5.7b Simple slopes analysis of the interaction between PGS x sexual abuse in probability of depression in adulthood

5.3.2.4 Study 2: Gene-environment correlation

The results of ordinal regression analyses with overall maltreatment or SLEs as outcome and PGS, sex, gender and 3 PCs as predictors, and linear regression analyses with specific maltreatments as outcome, showed there were no significant associations between polygenic scores of sensitivity and SLEs or childhood maltreatment (**Table 5.10**).

Table 5.10 Gene-environment correlations (Study 2)

	SLEs [a]		Overall maltreatment [a]		Sexual abuse [b]		Physical abuse [b]		Emotional abuse [b]		Physical neglect [b]		Emotional neglect [b]	
	OR	CI	*OR*	CI	β	CI	β	CI	β	CI	β	CI	β	CI
PGS1	1.01	.94, 1.09	1.20	.99, 1.44	.16	-.14, .47	.14	-.08, .36	.28	-.14, .69	.20	-.06, .46	.37	-.08, .82
PGS2	.97	.90, 1.04	1.11	.93, 1.33	.09	-.21, .38	.05	-.16, .26	.33	-.07, .73	.19	-.06, .44	.17	-.27, .60
PGS3	1.01	.94, 1.09	1.10	.92, 1.33	.08	-.23, .38	.12	-.10, .34	.28	-.14, .70	.11	-.15, .37	.27	-.18, .72
PGS4	1.03	.95, 1.10	1.11	.92, 1.34	.11	-.19, .41	-.02	-.24, .19	.23	-.18, .64	.00	-.26, .26	.38	-.07, .82
PGS5	.99	.92, 1.06	1.03	.86, 1.24	.11	-.18, .41	-.06	-.27, .16	.15	-.25, .56	.02	-.23, .28	.17	-.27, .61
PGS6	.99	.92, 1.06	1.07	.89, 1.29	.15	-.15, .45	-.02	-.23, .20	.25	-.16, .66	.05	-.20, .31	.27	-.17, .71
PGS7	.99	.92, 1.06	1.08	.90, 1.30	.13	-.17, .43	.03	-.18, .25	.25	-.15, .66	.05	-.21, .30	.31	-.13, .76
PGS8	.99	.92, 1.07	1.09	.90, 1.31	.16	-.14, .46	.03	-.18, .25	.30	-.11, .71	.05	-.21, .31	.32	-.13, .76
PGS9	.99	.92, 1.07	1.10	.92, 1.33	.20	-.10, .50	.03	-.19, .24	.32	-.08, .73	.07	-.19, .32	.32	-.12, .76

PGS= Polygenic score; SLEs= Stressful life events; OR= Odds ratio from ordinal regression model; β=beta coefficient from linear regression model; CI=95% confidence interval; CIs crossing 1 indicate non-significant OR and CIs crossing zero indicate non-significant beta; a= Ordinal regression model including overall maltreatment or SLEs as outcome and PGS, 3 PCs, age and gender as predictors; b=Linear regression model included the type of maltreatment as outcome, and PGS, 3 PCs, age and gender as predictors.

5.3.3 Study 3: Results

5.3.3.1 Study 3: Descriptive statistics

Descriptive statistics of the sample, including sample size, severity of anxiety symptoms at baseline and post treatment time points and for each diagnostic category are presented in **Table 5.11.** The results show mean score of anxiety symptoms at baseline was 6.20 (*SD*= .10), which decreased to 2.98 (*SD*= 2.11) immediately post treatment, indicating a positive effect of treatment on reducing anxiety symptoms. Similar reductions in anxiety symptom scores were observed across diagnostic categories at post-treatment.

The results of ANOVAs with PGS as the dependent variable and treatment type and diagnosis as independent variables suggested that PGS did not significantly differ by treatment type (e.g. $F_{(PGS1)}$= .70, p = .50) or diagnosis (e.g. $F_{(PGS1)}$=1.36, p= .25) at the baseline assessment. Similarly, there was no significant correlation between the PGS and baseline anxiety severity (r= -.03 to .03, p > .05). Overall, the results indicated that genetic sensitivity did not significantly bias treatment allocation and was not associated with specific anxiety diagnosis or pre-treatment severity of anxiety. There were also no significant associations between treatment type allocation and gender (X^2= 2.43, p = .30).

There were, however, significant associations between treatment type and symptom severity at baseline (F= 35.39, p < .001), between treatment type and age (F= 4.51, p= .01), and between treatment type and diagnosis (X^2= 69.76, p < .001) at baseline. The results suggest that younger participants and those with higher anxiety scores were more likely to be allocated to the more intensive treatments (individual CBT vs. group CBT vs. guided self-help CBT), and those with generalised anxiety disorder diagnosis were more likely to be offered group or guided self-help CBT treatment.

Table 5.11 Descriptive statistics of the sample (Study 3)

	Mean (*SD*) N				
	Baseline	Post treatment	Follow up1	Follow up2	Follow up3
Age	9.83 (2.20) 913 (m=417, f=496)				
Anxiety symptom severity: overall, by treatment and diagnosis					
Overall	6.20 (.10) 913	2.98 (2.11) 876	1.95 (2.35) 169	2.52 (1.95) 455	2.59 (2.25) 172
CBT	6.13 (1.04) 242	2.59 (2.20) 226	.90 (1.27) 40	2.10 (2.29) 93	2.53 (2.34) 125
Group CBT	6.41 (.98) 475	3.26 (2.01) 457	2.28 (2.52) 129	3.02 (1.68) 248	2.73 (2.02) 47
Guided self- help CBT	5.75 (.80) 196	2.75 (2.13) 193	. .	1.85 (1.92) 114	. .
Generalised anxiety disorder	6.19 (.90) 334	2.66 (1.88) 312	1.69 (2.09) 50	2.59 (1.74) 192	2.40 (2.24) 54
Social phobia	6.12 (1.01) 188	3.86 (1.92) 180	2.43 (2.64) 34	2.82 (1.93) 95	3.29 (2.09) 43
Specific phobia	6.28 (1.09) 102	3.19 (2.40) 100	2.09 (2.45) 27	2.34 (2.25) 53	2.25 (1.97) 22
Separation anxiety disorder	6.22 (1.02) 214	2.82 (2.20) 210	2.09 (2.41) 40	2.28 (2.04) 81	2.83 (2.48) 39
Other anxiety disorder	6.27 (1.12) 75	2.26 (2.14) 74	1.23 (2.21) 18	2.14 (2.32) 34	1.04 (1.80) 14

Of the total sample (*N*=913), 249 individuals had missing data on anxiety symptom severity at 3 time points, 578 at 2 time points, 77 at 1 time point and 9 individuals had no missing data

5.3.3.2 Study 3: The effects of the PGS of sensitivity on overall treatment response

Linear mixed models were used to investigate the effects of the PGS on overall treatment response (change in the anxiety severity) from baseline to the post treatment time points. These models included the fixed effects of the PGS as well as the fixed effects of diagnosis, 3 PCs, treatment type, baseline score, age, gender, and linear and quadratic effects of time. Repeated measures were accounted for by fitting random intercepts at the individual level. A further, higher-order, random intercept was fitted to account for the clustering of data within trials. The effects of demographic and clinical factors on treatment response were also examined separate models. The results indicated there were no significant effects of gender (β = .04, *p*= .37) or age (β = .01, *p*= .61) on treatment response. Higher symptom severity at baseline was associated with less favourable treatment response (β= .17, $p < .001$) and individuals with a specific phobia or social anxiety disorder diagnosis showed a significantly poorer response to treatment than those with generalized anxiety disorder (β= .20, *p*= .01 and β = .41, $p < .001$, respectively).

The effects of the PGS on treatment response are presented in **Table 5.12**. There were no significant associations between PGS of sensitivity and changes in anxiety scores post-treatment**.** Though not statistically significant, higher genetic sensitivity was inversely associated with anxiety score, indicating an overall more favourable treatment response for more genetically sensitive individuals.

Table 5.12 Association between PGS of sensitivity and changes in anxiety symptom severity post-treatment (Study3)

	β	CI	*p*
PGS1	.01	-.07, .09	.83
PGS2	.01	-.07, .09	.86
PGS3	-.02	-.10, .07	.67
PGS4	-.02	-.11, .06	.57
PGS5	-.03	-.11, .05	.43
PGS6	-.04	-.12, .04	.37
PGS7	-.03	-.11, .05	.49
PGS8	-.03	-.11, .05	.44
PGS9	-.03	-.11, .05	.42

PGS= Polygenic Score; β=beta coefficient from linear regression model; CI=95% Confidence interval; CIs crossing zero indicate non-significant beta; Mixed effects linear regression model with symptom severity at 4 time points as the outcome, and PGS, sex, age, linear and quadratic effect of time, baseline symptom severity, diagnosis, treatment type, 3 PCs as fixed effects, and individual and trial as random effects

5.3.3.3 Study 3: Treatment specific effects of the PGS of sensitivity

Linear mixed models were used to investigate treatment-specific effects of the PGS by fitting the same models as in the previous analyses but including a PGS by treatment interaction. A significant interaction in these models indicates that the PGS had a different effect on response according to treatment type. In these analyses there were no significant PGS by treatment interactions when comparing individual vs. guided self-help CBT or group vs. guided self-help CBT. However, significant treatment type-PGS interactions were identified when comparing individual CBT and group CBT (β_{PGS7}= .22, 95%CI [0.01-0.43], *p*= .04; β_{PGS8}= .21, 95%CI [0.01-0.42], *p*= .05; β_{PGS9}= .23, 95%CI [0.03-0.44], *p*= .03). The significant interaction term explained .12% of the variance in treatment response. These findings suggest that the effects of the PGS differed according to treatment type.

Post-hoc simple slopes analyses were conducted in order to probe these interaction effects, and further explore possible treatment specific effects of the PGS (see **Figure 5.8**). The results indicated that highly sensitive individuals responded more favorably to individual CBT, but worse to group CBT. The interaction was the inverse for low genetically sensitive individuals.

Linear mixed models were used to investigate treatment-specific effects of the PGS by examining the effects of PGs in each treatment group. In these analyses, similar models were fitted as in previous step (**5.3.3.2)** separately for patients treated with individual CBT, group CBT and guided self-help. As shown in **Table 5.13**, findings were non-significant for the PGS in each of these treatment groups, which was likely the result of a loss of power following stratification. Nevertheless, the PGS did appear to have different effects for the different treatment types, and consistent with findings from the interaction analyses, the largest differences were in individual CBT vs. group CBT. While higher genetic sensitivity was associated with a superior response to individual CBT, it predicted a poor response to group CBT (e.g. for PGS9: $\beta_{\text{individual CBT}}$ = -.08, $\beta_{\text{group CBT}}$= .11).

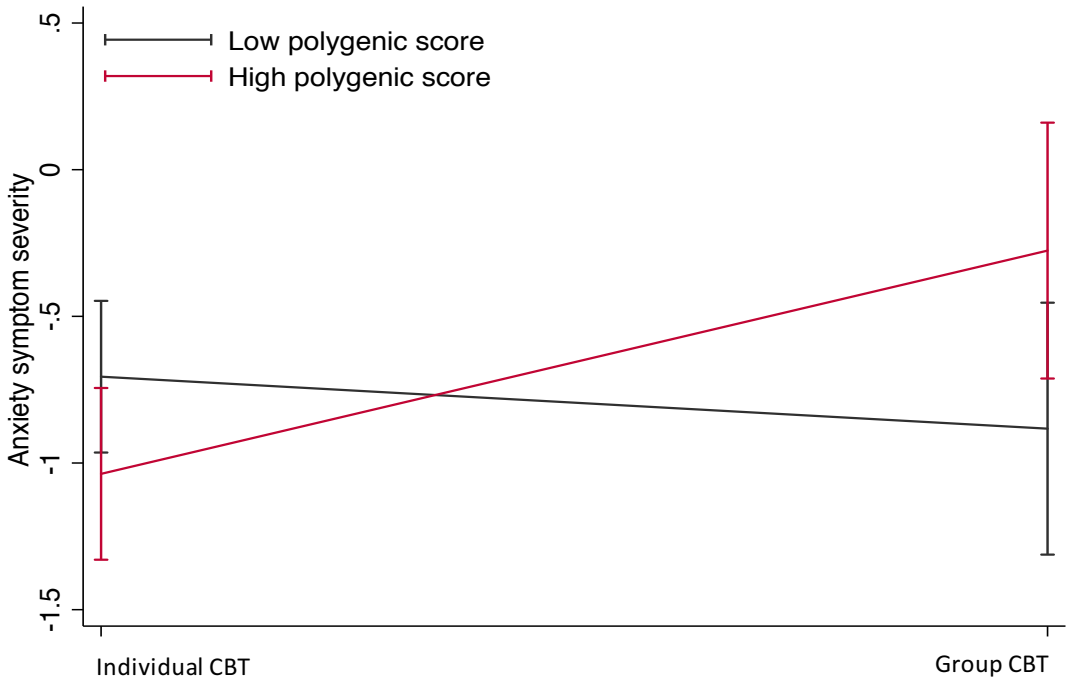


Figure 5.8 Simple slopes analysis of the interaction between PGS x treatment type predicting reduction in anxiety symptoms post treatment

Table 5.13 Association between PGS of sensitivity and changes in symptom severity post-treatment (Study 3)

	Individual CBT			Group CBT			Guided self-help CBT		
	β	CI	*p*	β	CI	*p*	β	CI	*p*
PGS1	.03	-.07, .12	.55	-.12	-.31, .07	.20	.12	-.02, .27	.10
PGS2	.02	-.09, .13	.73	.03	-.17, .22	.80	-.03	-.17, .11	.68
PGS3	.02	-.09, .13	.72	.01	-.18, .21	.89	-.06	-.21, .09	.41
PGS4	-.02	-.12, .09	.74	.06	-.15, .27	.56	-.04	-.18, .10	.57
PGS5	-.06	-.16, .04	.21	.05	-.14, .25	.60	-.05	-.21, .10	.51
PGS6	-.06	-.16, .04	.22	.05	-.16, .25	.66	-.05	-.21, .10	.52
PGS7	-.08	-.17, .02	.12	.09	-.12, .31	.39	-.03	-.19, .13	.68
PGS8	-.08	-.18, .02	.11	.09	-.12, .29	.40	-.04	-.20, .12	.61
PGS9	-.08	-.18, .02	.10	.11	-.09, .31	.29	-.06	-.21, .10	.49

PGS= Polygenic score; β=beta coefficient from linear regression model; CI=95% confidence interval; CIs crossing zero indicate non-significant beta; Mixed effects linear regression model with symptom severity at 4 time points as the outcome, and PGS, sex, age, linear and quadratic effect of time, baseline symptom severity, diagnosis, treatment type, 3 PCs as fixed effects, and individual and trial as random effects

5.4 Discussion

The main aim of this chapter was to examine whether genetic sensitivity moderates the effects of negative and positive environmental factors on mental health problems including response to treatment. This was explored using three separate studies, each aiming to specifically address the identified limitations and gaps in previous research as detailed in **Section 5.1.3**. A discussion of the findings is presented separately for each study, followed by implications, strength and limitations, and lastly, conclusions from research in this chapter.

5.4.1 Study 1: genetic sensitivity x childhood psychosocial environment interaction in predicting psychological distress across life span

This study examined how genetic sensitivity moderates the effects of the psychosocial environment on psychological distress across life span, in a prospective longitudinal cohort of over 2,800 individuals from age 7 to 52. The results suggested that genetically sensitive children who were exposed to unfavourable environments were at a higher risk of *concurrent* psychological distress than those with a low genetic sensitivity. However, this genetic sensitivity acted as a protective factor in the long-term, decreasing their risk of psychosocial distress in adulthood.

These intriguing results were contrary to expectations, since theoretical models of sensitivity suggest that genetic sensitivity acts for better and for worse, such that high genetic sensitivity in negative context would implicate worse outcomes and in positive context better outcomes and cross-sectional studies in the field have largely supported the hypothesised interaction pattern (Bakermans-Kranenburg & van IJzendoorn, 2011; van IJzendoorn, M. H. et al., 2012). However, the majority of the studies in the field are conducted with children and adolescents rather than adults (see **Table 4.1a** and **4.1b** in **Chapter 4, Section 4.1.2.2)**. It is possible that the hypothesised interaction pattern is more robustly detectable in childhood than is in adulthood, as the findings from the current study is consistent with previous environmental sensitivity findings in children, but adulthood findings were not. For example, Keers and Pluess (2017), using a subset of the data form the same study but a PGS of several candidate genes and material environmental quality in childhood and adulthood to predict adult psychosocial distress, did not find a significant GxE effect. Instead, they found a significant GxExE interaction, whereby genetically sensitive children were more vulnerable to adversity as

adults if they had experienced a poor childhood material environment, but were also significantly less vulnerable if their childhood material environment was high, compared to low sensitive individuals. Although Keers and Pluess (2017) study used longitudinal data, it is challenging to interpret the current study's findings with reference to this study, due to difference in measures of genetic sensitivity (candidate vs. genome-wide PGS) and environmental factor (material vs. psychosocial), but importantly because their analytical approach did not allow life-span examination of how sensitivity may differ as a function of time, or at childhood versus adulthood life stages. There is however at least one study examining the effects of *5-HTTLPR*, the most widely studied candidate sensitivity gene, and its interaction with early life stress (ELS) and age in predicting wellbeing. In one such study, Gartner et al. (2017) found that while the short allele (sensitivity genotype) was associated with lower levels of evaluative well-being in younger participants in the presence of ELS, this effect disappeared in middle-aged participants and the effects were reversed in old age. Similar to the findings in the current study, higher sensitivity (s-allele carriers) in the context of ELS was associated with lower levels of well-being in young age, but higher levels in older ages. The less sensitive individuals (l-allele carriers) reported lower levels of well-being in the presence of ELS. The authors interpreted the findings in the context of evidence showing short allele carriers are more receptive to social supports, and also display higher levels of social conformity(Homberg & Lesch, 2011; Kaufman et al., 2004); these traits inferred by the s-allele genotype may act as protective factors and promote successful adaptation to challenges of aging and therefor higher levels of wellbeing later in life.

It is difficult to draw on differential susceptibility theories to explain the unexpected results, since they are yet to make specific hypotheses about how the effects of sensitivity may differ as a function of time/aging. It is, however, possible to offer an appropriate interpretation of the results if the core features of highly sensitive personality are considered in light of theory and research on resilience/coping in response to adversity. Although contextual adversity/stress/childhood traumas are generally studied as risk factors for a range of psychopathologies including depression, there is great heterogeneity in response to these events (Rutter, 2007). In fact, it has been suggested that four types of reactions are likely following exposure to trauma/stressor (Connor & Davidson, 2003): first, the person may become maladjusted by using destructive means to cope with the trauma/stressor; second, the person may

overcome the stressor but show some deficits in functioning; third, the person may move forward beyond the trauma/stressor, returning to the same functioning as before the trauma; fourth, the trauma/stressor may present the person with an opportunity to grow and improve function in some respects. Rutter (1987) has suggested two alternative models of "stress sensitization " or "stress inoculation" to explain the heterogeneous outcomes of adverse experiences. In the first model, early adverse experiences predispose an individual to higher sensitization to future stressful events, whereas in the second model, the early traumatic/stressful experiences makes the individual more resilient to future stress events, as a result of meeting, and successfully coping with, challenges (Rutter & Rutter, 1993). The process via which one or the other outcomes may be observed is a dynamic and complex interplay between the person and the stressor's characteristics (Rutter, 2012). Research on the characteristics of the person in such processes have found that a cognitive redefinition of the traumatic/stressful experiences, a self-reflective style, taking considered approach to decision making, personal agency and a concern to overcome adversity are all important factors in shaping traumas/stressors into steeling/inoculation effects or even flourishing ones (Agaibi & Wilson, 2005; Hauser, Allen, & Golden, 2009; Rutter, 1985, 1987; Rutter, 1995). Considering the dynamic interplay between personal characteristics that influence the impact of environmental context on subsequent events, it is not surprising that developmentally distal and proximal environmental influences may have a different effect on psychological outcomes (Rutter, 2012). That is, while the immediate effects of adversity may lead to the conclusion that it was damaging, intervening factors and interactions over time may lead to different or even reversing of these effects.

The results from the current study seem to be best explained by a steeling effect of adversity, that has a greater influence on those with a high *vs*. low genetic sensitivity. This increased sensitivity to steeling effects is perhaps less surprising given that the core features of high sensitive personality involve deeper processing of emotional stimuli, greater self-reflection and introspection, extensive information processing and longer deliberation in decision making (Aron & Aron, 1997), all of which are deemed important in resilience/coping to adversity and more positive outcomes. Specifically, the results indicate that while heightened sensitivity predisposes the individual to higher psychological distress in childhood in response to low psychosocial environment quality, the inherent characteristics of high sensitive personality also potentiates lower psychological distress in later life. In contrast, low sensitive individuals may not be as

psychologically affected by the poor quality of their environment in childhood, but since they are also lower on the beneficial aspects of sensitivity, they do not learn as much from early exposure to such contexts (i.e. developing coping skills), leaving them ultimately more vulnerable to adversity later in life. The findings from the next study on depression and childhood trauma further support the conclusion of GxE results in the current study, a detailed discussion of which is presented in the following section. Overall, the results from this study indicate that the longitudinal effects of sensitivity differ across life-span, with high genetic sensitivity increasing risk for childhood psychological distress in the context of low quality childhood psychosocial environment in the short-term, but acting as a protective factor against adulthood psychological distress in the long-term.

5.4.2 Study 2: genetic sensitivity x childhood traumas and stressful life events interaction in predicting clinical depression

This study examined how genetic sensitivity moderates the effects of childhood maltreatment or recent stressful life events (SLEs) on major depression in a case-control design study of over 2,500 individuals. The results showed a significant main effect of SLEs and childhood maltreatment on depression. Higher number of SLEs were associated with two-fold increase in risk of depression, and the risk of depression was over four times greater for those who had experienced any maltreatment compared to those who had not, with the largest effect seen for physical neglect and abuse. There was a general trend towards higher risk of depression with increased genetic sensitivity, but the associations were not statistically significant.

With regards to SLEs, there were small but statistically non-significant interactions between PGS of sensitivity and recent SLE's in predicting the risk for depression. The interactions were in the expected direction. Specifically, the depressogenic effects of recent SLEs were greater in those with high vs low genetic sensitivity, whereas, in the context of low levels of adversity (few recent SLEs), the risk of depression did not differ by genetic sensitivity score. Though the interaction effects were not significant, this pattern of interaction is in accordance with differential susceptibility theories. That is, high genetic sensitivity would be associated with an increased risk of depressive symptoms in the context of adversity, but decreased/no difference in risk in low SLE contexts. The lack of significant effects in the current study may reflect the difference between the current study and previous GxE studies of environmental sensitivity in how

genetic sensitivity and the outcome are measured. Specifically, while much of the previous studies with SLEs have examined depressive symptoms and using candidate genes to index sensitivity (e.g. Priess-Groben & Hyde, 2013; Zimmermann et al., 2011), the current study was the first to examine *clinical depression*, using a genome-wide PGS of sensitivity. Interpreting the results in the context of these differences in outcome measure between previous and current study, it is possible that genetic sensitivity increases the risk of normally distributed depressive symptomatology in response to stressful life events, but it does not contribute sufficiently to risk for clinical depression; a qualitatively distinct phenotype compared to depressive symptoms; or that the previous studies are examining genetic sensitivity to risk of depression, rather than general genetic sensitivity to environments as captured here in the PGS score.

With regards to childhood maltreatment, there was evidence for significant interactions between genetic sensitivity and overall childhood maltreatment, and sexual abuse, though the pattern of interaction was contrary to expectations. While childhood maltreatment and genetic sensitivity were both found to increase the risk of depression, the combination of these factors resulted in a decreased risk. Specifically, the results indicated that in the absence of, or at low levels of childhood maltreatment, high sensitivity increased risk of depression in adulthood, but in the presence of severe maltreatment, genetic sensitivity acted as a *protective* factor. Low genetic sensitivity on the other hand was associated with an increase in risk of depression in the context of severe maltreatment.

The results are intriguing, especially in the context of previous research on sensitivity, showing that high genetic sensitivity increased risk of depressive symptoms in adolescence in the context of childhood maltreatment but decreased/no difference in risk in the absence of maltreatment, compared to low genetic sensitivity (e.g. Cicchetti et al., 2007). As noted earlier, the differences in results from the current study may reflect the differences in the outcome (clinical diagnosis vs. symptoms) and genetic (candidate vs. genome-wide) measure. It is possible that genetic sensitivity increases the risk of normally distributed depressive symptomatology, but that it acts as a protective factor when comparing the risk for clinical depression. Although this may explain why the results of the current study are different to others in the field so far, it does not explain why/how high genetic sensitivity decreases risk for clinical depression in the context of childhood maltreatment, and low genetic sensitivity increases the risk. A possible explanation comes to light when considering the results from Study 1, and

when comparing the interaction between maltreatment and genetic sensitivity to that of SLEs in the current study.

As it was evidenced in Study 1, the effects of genetic sensitivity changed over time, so that while the short-term effects in childhood were compatible with the differential susceptibility theories, the long-term effects in adulthood were reversed. Specifically, the more genetically sensitive children, compared to low genetically sensitive, were at higher risk of psychological distress when they grew up in less favourable psychosocial contexts, but that their genetic sensitivity acted as a protective factor in the long-term, decreasing their risk of psychosocial distress in adulthood. The results indicated an interaction with time, such that the passing of time between childhood events and genetic sensitivity moderated the risk for psychological distress. This pattern of interaction was explained in the context of steeling effects of adversity over time as a function of the highly sensitive person's characteristics. The same steeling effects appear to be in play for childhood maltreatment, consistent with findings for a range of psychopathologies including depression, as a function of personal characteristics noted earlier (Bulik, Prescott, & Kendler, 2001; Campbell-Sills, Cohan, & Stein, 2006; Cicchetti, Rogosch, Lynch, & Holt, 2009; Collishaw et al., 2007; Rutter, 1995; Valentine & Feinauer, 2007). Given that highly sensitive individuals may show more introspection and reflection, it is possible that low sensitive individuals do not process the emotional impact of the negative life events such as maltreatment, therefore at higher risk of developing depression later in life.

Additionally, while higher genetic sensitivity was associated with slight increased risk of depression in response to *recent* SLEs, it also acted, *in the longer term*, as a protective factor against clinical depression in the context of childhood maltreatment. The contrasting results may be due to the timing of the events, since SLEs were measured 6 months prior to depressive episode/diagnosis and maltreatment as the more distant childhood events. Though suggestive, it is difficult to firmly establish the differences in results are a function of time, and not SLEs vs. maltreatment effects, without further investigation in a longitudinal cohort. Overall, the results indicated that high genetic sensitivity is protective in the context of childhood maltreatment for risk of clinical depression, but it is not a significant contributor to risk for clinical depression in the context of high SLEs.

5.4.3 Study 3: genetic sensitivity x treatment interaction in predicting response to CBT intervention for paediatric anxiety disorders

This study examined how genetic sensitivity moderates response to psychological interventions for clinically diagnosed anxiety disorders in a sample of over 900 children. The treatment groups included individual CBT, group CBT, and guided self-help CBT. The results showed that treatment type was not a significant predictor of treatment response, whereby all individuals showed a reduction in their anxiety scores post-treatment, regardless of the treatment type they received. There were no statistically significant effects of genetic sensitivity on overall treatment response. However, as expected, there was a significant genetic sensitivity x treatment type interaction, whereby higher genetic sensitivity was associated with a good response to individual CBT, but a poor response to group CBT. Low genetic sensitivity showed the opposite pattern, whereby low genetic sensitivity was associated with a good response to group CBT and a poor response to individual CBT.

The result of the current study supports Keers et al. (2016) findings, by showing that genetic sensitivity moderates the outcomes of psychotherapeutic intervention for anxiety, with high genetic sensitivity associated with advantageous response to individual CBT versus group CBT. This finding is in line with differential susceptibility theories, which propose environmental factors (positive or negative) have a greater effect on more sensitive individuals, therefore the more sensitive individual may be more sensitive to the type of treatment they receive, compared to low sensitive individuals. The preferential response to more intensive type of treatment such as individualized CBT may reflect the fact that individuals with higher genetic sensitivity to the environment are more likely to develop the type of cognitive biases underlying anxiety disorders (such as a bias towards threat) (Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012), and therefore require more intensive treatments to overcome these biases.

While much of previous candidate sensitivity gene x treatment studies have found that genetically sensitive individuals may benefit disproportionately from psychological interventions for a range of outcomes including anxiety, depression, externalizing behaviours (Bakermans-Kranenburg et al., 2008; Brody, Beach, Philibert, Chen, & Murry, 2009; Eley et al., 2012), other studies have found preferential response to psychological treatments for low and not high genetic sensitivity for major depression (Cicchetti, Toth, & Handley, 2015) or bulimia (Steiger et al., 2008). The current study

also did not find a significant effect of overall treatment response for anxiety as a function of genotype. The differences may be due to the current study's use of a genome-wide PGS score of environmental sensitivity, CBT intervention type or the clinical sample, which has not been attempted in other environmental sensitivity studies so far, expect for Keers et al. (2016). On the other hand, the diversity of the results may also indicate that response to therapeutic interventions, as a function of genetic sensitivity may be disorder or treatment-type specific, and cautions against generalisation of the results to other treatment types or outcomes. Overall, the results of the current study suggest that the more genetically sensitive children respond better to individualised CBT treatment for reducing symptoms of a wide range of anxiety disorders.

5.4.4 Implications

The findings from the studies in the current chapter have several implications for research in environmental sensitivity. First, the results of Study 1 highlighted the importance of taking a developmental approach to GxE given that the effects of the interaction between environmental factors and genetic sensitivity differed across the life span. Importantly, since much of current differential susceptibility theories are based on evidence from cross-sectional studies or longitudinal studies in childhood, theoretical models of sensitivity would benefit from incorporating the current study's findings as starting point for extending the model to life-course development. Without considering a life course approach, our understating of genetic sensitivity to context may be skewed by the more immediate effects of environments, rather than their longer-term effects on an individual's mental health.

Second, the results of the study on genetic sensitivity, SLEs, and childhood maltreatment on risk for clinical depression highlighted the importance of studying sensitivity in the context of clinical diagnoses, and challenges the notion of high sensitivity leading to increased risk of mental health problems in adverse contexts. Using a genome-wide PGS of sensitivity, it was seen that contrary to expectations, high genetic sensitivity did not significantly increase risk for clinical depression in response to recent SLEs, and in fact acted as a protective factor against depression in response to childhood maltreatment. The findings therefore caution against generalising the findings from non-clinical samples to clinical samples. Most importantly, the findings with maltreatment show that the genetic factors underlying high sensitive personality entails

certain characteristics that reduce the risk for depression following childhood maltreatment, challenging the differential susceptibility theories' proposition that that high sensitivity increases risk for negative outcomes in response to adverse environmental influences. Specifically, it could be that in the short term and in response to immediate or recent adverse events, highly sensitive individuals have higher risk of mental health problems, but in the longer term, they are more protected than the low sensitive individuals.

Finally, the results of the study on response to CBT intervention for anxiety disorders, builds on existing research in therapygenetics, showing the "one size fits all approach" should be re-considered, as it was found that the efficacy of different treatment types differs according to the level of environmental sensitivity. High genetic sensitivity was associated with better response to individual CBT and worse response to group CBT, whereas low genetic sensitivity showed the opposite pattern. The findings may assist in deriving more success from interventions by targeting the interventions at the people most likely to benefit from it. For example, more intensive psychological treatment could be targeted at highly sensitive individuals, and the more cost-effective, lower-intensity approaches such as group-based therapies targeted at individuals with lower genetic sensitivity who may respond to them better or as effectively as they to individual CBT treatment.

5.4.5 Strengths and limitations

The studies included in the current chapter have several strengths. Firstly, all three studies used, for the first time, polygenic scores derived from genome-wide variants associated with sensitivity. Unlike candidate-gene based analyses or scores, using genome-wide polygenic scores is in concordance with our understanding of the polygenic nature of complex traits. Secondly, in constructing the polygenic score, genetic variants were included according to their evidenced association with general sensitivity to context, via high sensitive personality trait, rather than hypothesised candidate genes. Third, the studies in the current chapter were the first to take a life course approach to studying the interaction between polygenic score of genetic sensitivity and environmental influences in mental health, or examine the interaction patterns in relation to clinical depression.

Nevertheless, the findings should be interpreted in light of several limitations. First, the polygenic score of sensitivity was derived from a rather small sample (N=1,035), which

would affect its sensitivity and also the PGS was not examined for its association with environmental sensitivity in an independent sample, meaning it was difficult to determine the extent to which it might have captured environmental sensitivity in different study samples. It is possible therefore that the results reflect false positive or false negatives. The findings should therefore be considered preliminary and exploratory, pending replication in larger samples. Second, the measure of the environment in Study 1 was not a psychometrically standard measure of psychosocial environments, rather, an index of environmental factors deemed important in psychological functioning. Though its association with the outcome measure determined the validity of the measure, a psychometrically validated measure might have strengthened the results. Third, the environmental factor in Study 2 only included the extent of/presence and absence of negative context, and therefore not providing a full spectrum of both positive and negative environmental factors. Interpretation of the results may therefore be limited in their application to testing of response to more negative aspects of the environmental influences as a function of genetic sensitivity. Finally, the treatment allocation in Study 3 was not random, because the sample included children with anxiety disorders receiving psychological treatment as part of a trial, or treatment as usual in one of multiple studies; treatment type was therefore associated with several clinical and demographic characteristics at baseline. While inclusion of demographic and diagnostic variables in the analytical models, aimed to account for this, it does not exclude the possibility that the results were influenced by other unmeasured factors. The Replication of the results in a randomised trial, which better account for these confounds, would further validate the findings herein.

5.4.6 Future directions

First, other studies should address the limitations of the current research, including following up on the current findings, using genome-wide PGS scores of sensitivity, with a design that includes environmental factors from both positive and negative spectrum of events. Second, considering the findings of Study 1, it is important that theoretical models of environmental sensitivity are further developed to consider the lifespan implications of sensitivity. While the results of the study requires further replication, they provide encouragement for future research to investigate the mechanisms that underlie observed changes in the effects of genetic sensitivity on mental health outcomes. Specifically, future research may investigate what specific characteristics in the highly sensitive individuals, or the sensitivity genotypes, makes them more

susceptible to adversity in the short term, but acts as protective factors in the long-term. Following up on the results by asking whether these differences are a function of the same characteristics, or a constellation of different ones would have implications in understanding and promoting mental health. Third, in light of findings from Study 2, future research should aim to clarify if the trajectory of the interaction between genetic sensitivity and environmental exposures differs for clinical versus symptomatic presentation of mental health outcomes, and if genetic sensitivity shows specificity in its function according to the type of environmental factors (SLEs vs. maltreatment) being considered. This is an important future research direction, since current environmental sensitivity research tends to not distinguish between these outcomes and factors, and thus generalising the findings from one disorder/trait to others to provide evidence for the proposed function of genetic sensitivity. Insight provided by future research may help discern genetic factors that relate specifically to mental health in the context of specific environmental factors versus those that are more generic in their function. Finally, the findings from Study 3 are encouraging for the future research in environmental sensitivity; however, future research should address the limitations of the current study by using randomised trials in larger samples, as well as using patient records of response to other commonly prescribed therapeutic interventions to conduct genome-wide GxE studies. This enables researchers to examine if the treatment response differs as a function of genetic sensitivity and what works best for what type of disorders.

5.4.7 Conclusions

In conclusion, the studies in the current chapter were the first to examine how genetic sensitivity, indexed via genome-wide polygenic score of high sensitive personality, may moderate the effects of environmental factors on mental health across the life-span, in clinical depression, and in treatment response for anxiety disorders. The results of the life-span study of genetic sensitivity and the study of clinical depression both indicated that the effects of sensitivity differ across development. Specifically, adults and children with a high genetic sensitivity were more vulnerable to the effects of developmentally *proximal* adversity but more resilient to the effects of *distal* adversity. These findings suggest that genetic sensitivity may moderate processes by which early adversity lead to steeling or stress inoculation. The results of study on response to CBT therapy as function of genetic sensitivity, confirmed previous research findings that high genetic

sensitivity is associated with improved response to more intense treatment for anxiety disorders, such as individual CBT, rather than group CBT

Chapter 6

General discussion

Several recent theories (i.e. sensory processing sensitvity: Aron & Aron, 1997; differential suscceptibility hypothesis: Belsky, Bakermans-Kranenburg, et al., 2007; Belsky & Pluess, 2009; biological sensitivity to context: Boyce & Ellis, 2005), referred to here as differential susceptibility theories, suggest that individuals differ in their levels of sensitivity to their environmental contexts, and that those who are generally more sensitive tend to respond more positively to the beneficial aspects of their environmental, as well as being affected more detrimentally by the negative impact of adverse environmental influences (compared to less sensitivity individuals). Higher sensitivity therefore may be a risk factor for developing psychopathology in response to adversity, but also predict flourishing and lower risks in positive or health-promoting contexts. Individual differences in this environmental sensitivity, reflected in the "for better and for worse interaction pattern", are proposed to have a genetic basis. Although several candidate genes have been suggested to reflect environmental sensitivity, based on their for better and for worse moderating action on a range of environmental influences and outcomes in gene-environment interaction studies, the heritability of environmental sensitivity remains unknown. Additionally, bar one study by Keers et al. (2016), no studies to date have examined the genetic basis of sensitivity, using a quantifiable phenotype of environmental sensitivity, and genetic studies to date have almost entirely relied on candidate gene approaches.

The main purpose of this thesis was to examine the genetic basis of environmental sensitivity and its association with mental health outcomes. This was done by using the highly sensitive personality trait to index individual differences in environmental sensitivity and through a diverse range of analytical approaches. The main aims of this thesis were addressed through a series of studies presented in four chapters. A summary of the specific aims and findings from each chapter are presented below.

6.1 Summary of findings

6.1.2 Chapter 2

Aim: to develop and establish the psychometric properties of a new measure of environmental sensitivity suitable for use with children and adolescents.

While the Highly Sensitive Person scale (HSP; Aron & Aron, 1997) has been used as a quantifiable phenotype of environmental sensitivity in research with adults, there is no developmentally appropriate measure for studying environmental sensitivity at younger ages. Considering that the sample in the current thesis consisted mainly of children and

adolescents, developing a psychometrically valid measure for this population was an important first step towards the main aim of this thesis.

This aim was addressed across four studies in **Chapter 2**, via a large multi-site study in the UK, comprising of four independent samples (*N*= 1,931) of children and adolescents. In Study 1, the items for the new scale were selected from a larger pool of developmentally appropriate items that were deemed to capture the environmental sensitivity concept according to the adult measure, the Highly Sensitive Person scale by Aron and Aron (1997). Principal component analysis and confirmatory factor analysis was used to arrive at the final version of the scale, using a sample of 334 children. In Study 2, the psychometric properties of the new scale (highly sensitive child; HSC) were established by examining its associations with other relevant constructs in a sample of 11-year olds (*N*= 258). In Study 3, the test-retest reliability of the scale was established in a different sample of 10-year old children (*N*= 155). In Study 4, the psychometric properties of the new scale were examined in a large sample of adolescents (*N*= 1,174).

The results across the different samples indicated that the newly developed HSC measure reflected the same structure as the adult measure by showing the same three underlying factors of ease of excitation (EOE), aesthetic sensitivity (AES), and low sensory threshold (LST). Factor analysis results across the studies indicated that a bi-factorial solution fitted the data best, such that the 12 items reflected three components but also loaded onto a general factor of environmental sensitivity. The scale also showed good internal consistency and test-retest reliability. In addition, the measure was associated in meaningful ways with other constructs, as seen with the adult scale and as theorised in the initial conceptualisation of the phenotype. Higher scores on the scale, reflecting higher levels of environmental sensitivity, were associated with higher behavioural inhibition and activation, positive and negative affect, effortful control, neuroticism and lower extraversion. The observed correlations between the total score and both BIS and BAS, as well as both negative and positive emotionality, suggested that this phenotype encompasses sensitivity to both negative and positive influences, consistent with differential susceptibility theories.

Associations of the three subscales of sensitivity with other measures were in line with previous research findings in adults, showing that while the AES component was more strongly associated with measures that reflect sensitivity to more positive experiences (e.g. BAS, positive emotionality, extraversion, openness, conscientiousness), EOE and

LST were more strongly associated with traits that reflect sensitivity to negative environmental factors (e.g. BIS, negative emotionality, negative affect, and neuroticism). The findings from this chapter have since been published (Pluess et al., 2018), and the scale has been used in various studies with children and adolescents. The findings from these studies further strengthened the validity of this scale, by showing that environmental sensitivity as captured by this measure moderates the effects of environmental influences for better and for worse (e.g. Nocentini et al., 2018; Slagt et al., 2018).

6.1.3 Chapter 3

Aim: to examine the heritability of environmental sensitivity and its genetic architecture as a function of its components and its relationship with other traits.

While candidate GxE studies have found several genetic variants that reflect sensitivity to environmental influences by moderating the impact of negative and positive environmental exposures on a range of outcome, no studies to date have examined the total genetic contribution to individual differences in environmental sensitivity.

This aim for this chapter was addressed by examining the heritability of environmental sensitivity, for the first time, using twin design and the scale developed in the previous chapter, in a sample of adolescent twins from the UK (*N*= 2,868). Following on from the findings from the previous chapter, multivariate twin design was used to examine whether the genetic influences underlying variations in environmental sensitivity reflected one common factor shared between all three components of the scale, or if there were also some genetic influences that were distinct to each trait. In addition, multivariate models were used to examine the extent to which the correlation between environmental sensitivity and the Big-Five personality traits, as well as depression and anxiety were due to shared genetic or environmental influences. The results confirmed the hypothesised genetic basis of environmental sensitivity, by showing that genetic influences explain almost half (47%, 95% CI= 30, 53) of the variation in environmental sensitivity. The heritability was found to be mostly due to additive genetic effects, and no significant sex differences were observed in heritability estimates. The multivariate analysis results revealed, as expected based on results from **Chapter 2**, that the three factors of environmental sensitivity contributed to a common latent factor, and that variations in the three components were partly explained by shared genetic and environmental influences underlying all three factors, but also distinct genetic and

environment influences that were specific to AES and LST components. The results suggested that the genetic factors underlying variations in environmental sensitivity may be best understood as the function of two sets of genetic influences, those that give rise to variations in overall levels of sensitivity (i.e. common latent factor), and those that reflect variations in sensitivity to specific type of environmental influences: negative aspects of environmental influences (as reflected in the LST component) and positive aspects of the environment (as reflected in the AES component). This interpretation is also consistent with the hypthesised existence of different types of sensitivity (Pluess, 2015) as reflected in diathesis-stress (negative sensitivity), vantage sensitivity (positive sensitivity) and differential susceptibility (general sensitivity to both positive and negative).

Analysis of the aetiological overlap between environmental sensitivity and personality traits, as well as depression and anxiety revealed a large genetic overlap between the genetic factors that explain variations in environmental sensitivity and neuroticism and extraversion (approx. 80%). However, the environmental factors that explain variation in these phenotypes were found to be distinct to each. The genetic influences on environmental sensitivity were also shared with those underlying depression and anxiety, though to a lesser extent (approx. 47%). There was a small overlap of the environmental factors that explain the variations in depression, anxiety and environmental sensitivity (approx. 10%). Overall, approximately one third of the genetic and environmental influences on environmental sensitivity were shared with depression and anxiety, and two thirds were unique to it.

6.1.4 Chapter 4

Aim: to identify the molecular genetic factors associated with individual differences in environmental sensitivity

Previous studies have identified genetic variants that moderate the impact of environmental influences in a manner consistent with differential susceptibility theories (i.e. for better and for worse). However, no studies to date, with the exception of one (Chen et al., 2011), have examined how these sensitivity candidate genes relate to individual differences in the phenotype of environmental sensitivity (i.e. HSP). In addition, previous studies on environmental sensitivity focused almost exclusively on candidate gene approaches, rather than exploratory genome-wide approaches.

The aims in this chapter were examined by applying two different approaches. In the first part, the candidate gene approach was used to examine the associations between five sensitivity candidate gene variants (*MAOA, 5-HTTLPR, DRD4, DAT1, STin2*) identified in previous research. Next, gene-based analyses were applied to examine the association between 20 candidate genes and environmental sensitivity at the gene rather than the SNP level. Analyses were conducted across 3 independent samples, one from Belgium (*N*= 838), plus two from the UK (*N*= 395 and *N*= 642). In the second part, genome-wide approaches were employed to conduct a GWAS of environmental sensitivity across two samples from the UK, as well as a meta-analysis of the data to identify those SNPs most strongly associated with variations in environmental sensitivity. In addition, genome-wide gene-based and gene-set analyses were conducted. Finally, genome-wide polygenic score analysis was conducted to examine whether a polygenic score of environmental sensitivity predicts sensitivity in independent samples, and also to test whether polygenic scores from 13 other related phenotypes (i.e. Big-Five personality traits, autism, ADHD, anxiety, depression, insomnia, loneliness, subjective wellbeing, educational attainment) would predict variations in environmental sensitivity.

The candidate gene approach did not yield evidence of a significant association between sensitivity candidate gene variants (or genes) and individual differences in environmental sensitivity across the three samples. This was despite the larger sample sizes of the current studies, rendering them more powerful to detect the effect sizes reported in previous GxE studies from which the candidate genes were selected. The findings therefore indicate that despite previous GxE studies regarding these candidate variants/genes as sensitivity genes, they may not play a significant role in explaining individual differences in the phenotype of environmental sensitivity. It is also possible that they explain a very small proportion of variance in sensitivity, and therefore require larger samples to detect these small effects.

The genome-wide approach resulted in mixed findings. There were no SNPs associated with environmental sensitivity at genome-wide significance level, which was expected due to the small underpowered samples in the current studies. Gene-based and gene-set analyses did identify Ladybird Homeobox 1 gene (*LBX1*) in Chromosome 10 and the PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY gene-set to be significantly associated with variations in environmental sensitivity, therefore proposing potential new candidate genes and biological mechanisms related to this phenotype.

These associations, however, failed to replicate in the other sample, again reflecting the low power in these studies. The polygenic score analyses proved more successful with. results suggesting that the polygenic score of environmental sensitivity from the UK discovery sample predicted 1% of the variance in the other independent UK sample. According to the cross-trait polygenic score analyses of thirteen phenotypes from large GWAS studies, there were robust associations between the phenotype of environmental sensitivity and the polygenic scores of neuroticism, anxiety, autism, openness, extraversion, depression, with the latter four being robust to significance threshold correction for multiple testing, and explaining 2-3% of the variance in environmental sensitivity. Polygenic score analysis is a powerful approach, since the discovery sample is fully independent of the target sample and there are no shared environmental factors. Hence, any observed association between a trait and a genetic predictor (based on the discovery sample) must be due to shared genetic factors. The findings from the polygenic score analyses in this chapter support the twin model findings from **Chapter 3**, suggesting that environmental sensitivity shares some of its genetic aetiology with other traits including depression, anxiety, neuroticism, and extraversion.

6.1.5 Chapter 5

Aim: to examine the moderating effects of genetic environmental sensitivity on the association between environmental influences and mental health outcomes

Differential susceptibly theories propose that individuals that are more sensitive fare worse in negative contexts (compared to less sensitive individuals), but also benefit more from the positive/protective aspects of positive environmental exposures. Three independent studies were conducted to examine the main aim of this chapter, using the polygenic score of sensitivity obtained from the previous chapter as an index of genetic sensitivity.

In Study 1 it was examined whether genetic sensitivity moderates the impact of childhood psychosocial environmental quality on psychological distress across the life course. This was done using longitudinal data and conducting linear mixed model analyses, to examine the moderating effects of the polygenic score of sensitivity on psychological distress for 2,800 individuals from childhood to adulthood (ages 7 to 50).

Study 2 aimed at examining the moderating effects of genetic sensitivity on the well-established association between childhood maltreatment as well as stressful life events

(SLEs) and clinically ascertained major depressive disorder in a sample of 2,500 individuals.

In Study 3 the focus was on the moderating effects of genetic sensitivity in response to three types of psychological interventions that vary in intensity (individual CBT, group CBT and guided self-help) in a sample of 900 children with clinically diagnosed anxiety disorders. Linear mixed model analysis was applied to examine changes in symptoms post treatment as a function of genetic sensitivity and the type of treatment received.

The results of Study 1 indicated that the moderating effects of genetic sensitivity changed across life span. Specifically, those children who were highly sensitive and experienced poor quality psychosocial environment showed *higher* levels of psychological distress environment in childhood, but *lower* levels when growing up in higher quality environment; an interaction pattern consistent with differential susceptibility theory. However, the moderating effects of genetic sensitivity changed as a function of time, such that highly sensitive children who experienced poor psychosocial environments in childhood, were at *lower* risk of psychological distress in adulthood (compared to low sensitive children). In other words, for highly sensitive individuals, poor quality childhood environment was a risk factor in childhood, but acted as a *protective* factor in adulthood. The findings appear to indicate that the moderating effects of genetic environmental sensitivity may be contingent on the specific developmental period and that its distal versus proximal effect may differ across life span. More specifically, while poor psychosocial environmental quality in early childhood, marked by lower parental support, may hamper the psychological functioning of the genetically sensitive child in the short-term, it may also forster the development of protective traits, such as self-efficacy on the longer term, which then contribute to elevated resilience in adulthood (i.e. psychological immune system, "steeling" effects). Perhaps, the hypothesised ability of genetically sensitive individuals to process information and emotions to a greater depth and deliberation in making decisions may lead to higher levels of distress in the adverse context, in the short term, but also lead to greater learning, more efficient strategies for dealing with future stressful events in the long-term. This interpretation is in line with stress inoculation/ steeling theory (Rutter, 1987), according to which exposure to adverse environmental factors lead to more resilience in response to future adversity.

The results of Study 2 showed that there were no significant effects of genetic sensitivity in response to recent SLEs regarding the risk of major depression, though the

direction of effects was consistent with differential susceptibility: More sensitive individuals (compared to less sensitive) had a higher risk of experiencing a depressive episode in response to recent SLEs and lower risk in the absence/low levels of SLEs. For childhood trauma, the results were in line with Study 1, such that the effect of childhood maltreatment for genetically more sensitive individuals was protective in terms of risk for developing major depression in adulthood. The different moderating effects of genetic sensitivity for SLE and maltreatment on the outcome may reflect the findings from Study 1, such that the effects of distal (childhood maltreatment) versus proximal (recent SLEs) environmental influences are different for more sensitive individuals, perhaps as a function of the inherent characteristics of higher sensitivity promoting resilience in the longer term (i.e. steeling effects).

The results of Study 3 showed that highly sensitive individuals were more discriminant in their response to psychological intervention than less sensitive individuals. While most participants benefited from receiving treatment (i.e. decrease in anxiety symptoms) regardless of their level of sensitivity or the type of treatment received, the more sensitive individuals showed a stronger response to more intensive types of treatment, such as individual CBT versus group CBT. The findings suggest that more genetically sensitive individuals may benefit more from more personalised types of CBT treatment.

6.2 Implications

The implications of the various findings from this thesis are discussed from two perspectives: First, in relation to environmental sensitivity theory and research, and second, in the wider context of psychological research and practice.

6.2.1 Implications for environmental sensitivity research and theory

New candidate genes underlying environmental sensitivity. Although the results of the GWAS, gene-based and gene-system analyses have to be considered preliminary and exploratory, due to the low power in these studies, the results propose potential new systems and genes implicated in the aetiology of environmental sensitivity. The gene-system results particularly highlighted that genes other than those relating to serotonin and dopamine systems (i.e. *LBX1* and biological processes implicated in embryonic development, cell differentiation and apoptosis) may be implicated in the mechanisms underlying individual differences in sensitivity, and should encourage follow up research on these alternative genetic factors implicated in this trait.

The relationship between environmental sensitivity and other traits. The observed genetic correlations between environmental sensitivity and related traits may give an indication of how they are relevant to each other and why they are associated. The genetic overlap can be interpreted in two distinct ways: First, these correlating genetic factors may predispose an individual to be more susceptible to environmental influences (e.g. stressful life events), which along with the presence of other trait-specific genetic factors, contribute to the development of the associated phenotype (e.g. neuroticism). According to this model, environmental sensitivity genes moderate the effects of specific environmental influences on the associated trait and are therefore involved in its development. The genetic correlation thus explains some of the observed phenotypic correlation, but environmental sensitivity and the associated phenotype still remain distinct phenotypes. Second, these genetic factors may reflect the shared biological precursors of two distinct phenotypes, each manifested as a function of specific/separate sets of genetic and environmental influences. In this model, environmental sensitivity is not a significant factor in the development of the other phenotype, but they co-occur due to their correlating genetic influences. It is hard to determine, through the type of analysis conducted here, which model may best explain the observed correlations. However, the first hypothesis has been initially explored in the earliest theoretical models of highly sensitive personality and its commonly observed association with the traits of neuroticism and introversion (low extraversion). The hypothesised model has been fully detailed in **Chapter 2, Section 2.1.1**, but will be presented here again briefly.

Association with high neuroticism and low extraversion: According to sensory processing sensitivity theory (Aron & Aron, 1997), highly sensitive individuals have an inherently lower threshold of reactivity to sensory stimuli, as well as greater awareness and deeper processing of sensory and psychological stimuli. The tendency for lower threshold of reactivity to sensory stimuli, and higher attention capture by a larger number of salient stimuli and therefore larger processing load can lead to overstimulation and suboptimal response (e.g. slower, less accurate). In addition, more complex and discriminating stimuli-processing style can lead to temporary pauses, or inhibitions of behaviour (e.g. more deliberation, reflecting before acting). Such inherent tendencies in processing of environmental stimuli could give rise to psychological and behavioural characteristics such as being easily overwhelmed by sensory and psychological stimuli, behavioural inhibition (or pausing to reflect when faced with novel situations), greater attention to detail, and intensity in feelings of pleasure or discomfort. This could explain why introversion (or low extroversion) and neuroticism

are more pronounced in highly sensitive individuals, with the former as a strategy to avoid overstimulation and the latter as a consequence of the interaction between inherent sensitivity and aversive experiences. Specifically, Aron and Aron (1997) suggest that while low sociability can be a consequence of aversive social and attachment experiences, it can also be a consequence of high sensitivity, whereby low sociability develops over time as an adaptive response to avoid overstimulation. This is because social situations tend to be highly stimulating contexts due to their characteristic novelty, unpredictability and complexity. Higher arousal due to higher sensitivity to stimulation can overwhelm the individual and lead to poor performance in such situation, leading to discomfort in and avoidance of social situations. High sensitivity in the context of adverse environmental experiences can lead to neuroticism, since retrospective evaluations following experiencing aversive stimuli is conducted more deeply and in greater detail, leading also to greater awareness of potential threat cues in prospective evaluation of danger and ensuing preoccupation with danger and mitigating actions. A similar pathway has been proposed for depression/negative affect and anxiety.

Association with Autism: With regards to the correlation between environmental sensitivity and autism, no hypothesis have yet been suggested, but it is true that more sensitive individuals and autistic individuals tend to report higher levels of unpleasant or distressing reactions to overstimulation from sensory inputs. The genetic correlations between these traits may reflect the genetic factors that are shared between these traits that lead to presentation of heightened sensitivity to environmental stimuli, whereas the presence or absence of other genetic factors may lead to the presentation of other symptoms that together make up the symptomology of autism.

Association with openness and wellbeing: It is less clear what mechanisms may best explain the genetic correlation of environmental sensitivity with openness and subjective wellbeing. It is possible that heightened sensitivity creates a larger repertoire of impact by various kinds of environmental influences, including positive ones, which lead to positive reinforcements for being generally more open to experiences. Regarding the observed correlation between lower sensitivity and higher wellbeing, low sensitivity may act as a generally protective factor during the human life span, which undoubtedly is never entirely free of stressors and commonly includes some degree of traumas and stressors. It is important to emphasise that until further experimental research is conducted the interpretation of genetic correlations remain speculative.

Developmental specificity in environmental sensitivity: Findings from **Chapter 5**, implicated developmental specificity regarding the effects of environmental sensitivity, such that the function of sensitivity to context in childhood may be different to that in adulthood. Specifically, genetic environmental sensitivity may not always function in a "for better and for worse manner" across life span. The findings were consistent with the notion of steeling effects, or desensitisation to the effects of adversity, as a function of the interaction between genetic sensitivity and lower childhood environmental quality. Perhaps, the ability of genetically more sensitive individuals to process information and emotions to greater depth, leads to their higher levels of distress in adverse contexts, but also to greater learning and the acquisition of effective strategies for coping with future stressful events. The results may also reflect gene-environment correlation. Since genetically sensitive individuals are more affected by their environmental contexts, they are also more likely to self-select into the type of environments that are better suited to them as they mature; their higher genetic sensitivity therefore acts as a protective factor later in life. The main implication of these findings for future research on environmental sensitivity is that it is crucial to consider development across the life span. Current theories may lead to the assumption that genetic sensitivity functions consistently in a "for better and for worse" manner across life, but this is not supported by the findings reported in this thesis.

6.2.2 Implications for psychological research and practice

The majority of GxE studies have been conducted from a diathesis-stress perspective, which requires re-evaluation in light of differential susceptibility research suggesting that many of the common genetic variants in these studies may reflect generally heightened susceptibility to both negative and positive environmental influences, rather than exclusively vulnerability. Incorporating environmental sensitivity research findings is therefore crucial in order to accurately interpret the role of genetic factors in common mental disorder as well as wellbeing outcomes.

The differential susceptibility framework for GxE is not necessarily competitive or contrary in explaining the interaction between genotype and environment on outcomes. Indeed, it is possible that genetic risk for psychiatric disorders includes a combination of genetic variants that operate in a variety of ways. That is, genetic risk for a psychiatric disorder may include variants that have a direct effect on the psychiatric

disorder, variants that exclusively increase risk by increasing sensitivity to adversity (i.e. vulnerability), variants that increase risk by decreasing sensitivity to protective factors such as social support (i.e. vantage resistance), and variants that increase sensitivity to both adverse and protective environments (i.e. differential susceptibility). While there is no research to date that has examined such an integrated genetic model, current empirical evidence supports the existence and relevance of all three GxE interaction models as explanation for the observed link between environmental factors, genotype and mental health outcomes. Hence, considering the various ways in which genetic factors may interact with environmental influences to bring about mental health problems or protect against them should be an important feature in mental health genetic research.

Considering GxE findings showing that high sensitivity acts as a protective factor against future stressors, resilience research may particularly benefit from studying genetic sensitivity as a potential characteristic that moderates the developmental trajectory in response to contextual adversity. While the current study examined the associations at the genetic level, the findings should encourage paying greater attention to understanding this personality trait as an important individual characteristic for a range of outcomes. Understanding what specific characteristics of highly sensitive individuals can act as protective factors in response to adversity may inform interventions.

Finally, the findings on treatment response showed that more genetically sensitive individuals varied more strongly in their response to the type of treatment they received (better response to individual CBT vs. group CBT), regardless of their symptoms severity or anxiety disorder diagnosis. Interestingly, the intervention outcome did not differ as a function of treatment type for genetically less sensitive individuals. These findings, pending further replication, may be incorporated in clinical practice by considering an individual's personality trait (as indicator of underlying genetic sensitivity) as an important factor when deciding on individual treatment. The current National Institute for Health and Care Excellence (NICE) guidelines, for example, are based on a stepped care approach (National Institute for Health and Care Excellence, 2013), which takes into account the severity of the anxiety disorder, with more severe symptomology receiving more intensive types of psychological intervention. Incorporating differences in environmental sensitivity in this model of care when

formulating individualised intervention plans is an important potential application of the current findings.

6.3 Strengths and limitations

The following section considers the strengths and limitations of the research carried out in this thesis with reference to the main aims of this thesis.

Aim 1: Develop and use the phenotypic measure of environmental sensitivity to explore the hypothesised genetic basis of sensitivity

Strengths: One of the main strengths of the studies conducted here was access to a phenotype of sensitivity. This is important given two main disadvantages of studying sensitivity as an operationally defined construct in order to identify genes based on their moderating action alone. First, the GxE findings to date may not necessarily reflect general sensitivity to environmental contexts, but rather represent variations in sensitivity to specific environmental influences, related to specific outcomes. This is because, as noted in **Chapter 1** and **Chapter 4**, the majority of studies to date have examined specific candidate genes in the contexts of specific outcomes and environmental influences (e.g. *5-HTTLPR*, stressful life events, depression), and do not allow to determine whether the findings can be extended to reflect *general* sensitivity to context, as differential susceptibility theories propose. Second, variations in environmental sensitivity may not be accurately captured by the study design, because such studies rely heavily on two implicit assumptions: i) that reactivity to environmental influences always leads to overt measureable responses (e.g. development of depression symptom or not), and ii) that the response to the environment can be narrowly defined to the one that is measured in the study (e.g. variations in depression) and thus dismissing other potential outcomes of the environmental exposure (e.g. anxiety rather than depression). The latter is specially important since it has been demonstrated in studies of diverse types of risk factors and outcomes, that any risk factor may produce a variety of outcomes (i.e. Cicchetti & Rogosch, 1996). The implication of these implicit assumptions is that unobserved or unmeasured responses in these studies are misclassified as no reactivity/response and no difference in interaction with the environment. An example from another area of research may make the latter point clearer. Consider for example the research evidencing peer victimization is an established risk factor for internalising disorders (Boivin, Hymel, & Bukowski, 1995), though not all individuals exposed to it develop internalising disorders. While one may

conclude that those who do not develop internalising problems are immune to the effects of peer victimisation, research considering multiple alternative outcomes have found several differential trajectories following peer victimisation, including externalising problems, high achieving and low achieving, as well as internalising problems (Hanish & Guerra, 2002). Therefore, it may not be so much that a risk factor has no effect on some individuals, but that for a subset of individuals it has an alternative effect to what is generally expected and measured. Similarly, in an operational model of sensitivity, unmeasured differential response to a specific environmental factor may be misclassified as low sensitivity.

Using a phenotype of sensitivity can account for this, since the phenotypic approach defines environmental sensitivity as a function of *characteristic* responses and *general tendencies* that reflect sensitivity to a broad range of contexts, rather relying on capturing responses at a particular time in a specific context, or assuming that if the response is not manifested in the outcome of interest then it does not exist. The phenotype conceptualisation of environmental sensitivity also entails certain limitations, for example, the difficulty in reliably capturing such a complex phenotype via self-report or other report questionnaires. Notwithstanding this limitation, using the phenotype of environmental sensitivity when identifying the genetic factors that underlie environmental sensitivity may be more appropriate than using genetic markers of environmental sensitivity in an operational design.

Limitations: One limitation of the HSC measure is that it is based on self-report; therefore it is a subjective index of environmental sensitivity. Using other report or more objective measures of sensitivity would complement and strengthen the findings.

Aim 2: examine the genetic basis of environmental sensitivity and identify molecular genetic factors underlying its individual differences.

Strengths: The studies in the current thesis applied a wide range of methodologies to examine the genetics of environmental sensitivity. Some of the analyses in the thesis were used for the first time in research on environmental sensitivity, attempting to find novel results using a range of established and more recent methodological approaches that have proved successful in research with other phenotypes. For example, classic twin modelling was used to derive the heritability estimates for environmental sensitivity and examine its genetic architecture and relationship with other relevant traits. The molecular genome-wide approaches, explored the genetic basis of sensitivity

at both SNP as well as gene and gene-system levels, and conducted polygenic score analysis of environmental sensitivity in a meta-analysed sample. The large sample sizes used in the heritability analyses ensured sufficient power to detect the expected effects. Conducting the molecular genetic analysis in multiple samples and meta-analysis of the data ensured increased power and sensitivity for the polygenic score analysis.

Limitations: First, all measures used for the heritability studies were self-report questionnaires, which could have inflated the cross trait correlations. Using different informant sources would have accounted for this bias. Second, although genome-wide approaches address one of the main limitations of candidate gene studies (i.e. the requirement for a-priori hypothesis regarding functional relevance of the genes to the trait), this hypothesis-free approach presents two challenges: increased rates of false positive and false negative results. This is because in genome-wide association studies, typically over 1 million SNPs are tested for their association with the trait, therefore creating a multiple testing problem with increased possibility of type I error (false positive results). In order to counter against false positive results, the significance threshold for genome-wide findings are commonly adjusted to $p < 5 \times 10\text{-}8$ (Pe'er, Yelensky, Altshuler, & Daly, 2008). While the correction for multiple testing addresses the type I error rates, it also increases the possibility of type II errors (false negative results), if the sample does not provide the power to detect the very small effect sizes at this high significance threshold. Since GWAS examines the main effects of common variants on the trait, and the effect sizes of single SNPs are expected to be very small (< .01%), adequately powered samples (N > 1 million) are required to address the false negative finding results (Visscher et al., 2017). Hence, the GWAS analyses in the current thesis were clearly underpowered due to the small sample sizes. Similarly, the genome-wide gene-based and gene-set analyses were underpowered when correcting for multiple testing. Polygenic score approaches do not necessitate the same stringent criteria for multiple testing correction, because the SNPs are not considered for the singular contribution to the trait. However, the low power to detect small effects of SNP on the trait at the first stage of polygenic score construction (GWAS of the discovery sample) would have impacted the down-stream processes when SNPs summary statistics are used to construct the polygenic score. Third, while polygenic approaches have been more successful in predicting the genetic risk/propensity for the examined trait, this approach is lacking in promoting knowledge of the biological processes underlying the disease, since the biological correlates of the SNPs in the PGS were not further explored. Fourth, the molecular approaches only considered additive genetic

effects. Meta-analysis results of Polderman et al. (2015) suggest that additive genetic effects explain only 2/3 of the heritability of complex traits, with the remaining 1/3rd accounted for by non-additive effects. Results of model fittings from heritability analyses indicated that the effects are mostly due to additive genetic effects, but there also exists some non-additive genetic effects, as indicated by higher than twice MZ twin correlations compared to DZ twins.

Aim 3: Examine the effects of environmental sensitivity genetics on mental health outcomes

Strengths: The moderating effects of genetic sensitivity were examined across the life span, using a longitudinal design to examine changes within individuals, rather than relying on cross-sectional data. Furthermore, the studies included a PGS of environmental sensitivity based on genome-wide variants, which may better index sensitivity than single candidate genes, and PGS may reflect general sensitivity rather than specific sensitivity to specific contexts. A further strength is the use of clinically diagnosed disorders in two studies, rather than symptoms, addressing a gap in research on environmental sensitivity and clinical disorders.

Limitation: The PGS derived from meta-analysed GWAS in **Chapter 4** and used for GxE analyses in **Chapter 5** were likely to be noisy, due to the small GWAS at the first step, therefore not capturing environmental sensitivity in a precise way. Also, due to not having data on the environmental sensitivity phenotype in any of the samples in **Chapter 5**, it was not possible to examine how well the PGS predicted environmental sensitivity in these independent samples. In addition, the environmental measures in Study 2 and Study 3 did not always stretch from the extremes of negative to the positive end of the quality spectrum, therefore limiting the extent to which variations in environmental sensitivity may manifest themselves in a for better and for worse pattern in these studies.

6.4 Future directions

First, the heritability results using twin design provided a first estimate of heritability for environmental sensitivity. Since twin model derived heritability are proposed to estimate an upper limit of heritability, future research should consider alternative approaches such as SNP-based heritability analyses, to obtain a lower limit of heritability. In addition, since the contribution of genetic influences on other phenotypes has been reported to change over time (Gow et al., 2011; Haworth et al., 2008), future

studies could examine the stability of heritability of environmental sensitivity over time. This is practically of interest, since the effects of genetic sensitivity appeared to decrease and change over time in the life span GxE study of sensitivity and psychosocial distress in **Chapter 5**. In addition, future research should examine the specific environmental factors that contribute to individual differences in environmental sensitivity, especially because the results indicated that more than half of the variation in sensitivity is due to environmental factors.

Second, twin model results showed that individual differences in environmental sensitivity might be a function of three distinct genetic/biological systems that could result in different sensitivity types, depending on the proportional representation of these genetic factors underlying each component. Future research could further explore these preliminary findings, by examining whether the associations between the genetic factors related to different components of sensitivity relates to other outcomes in expected ways. For example, AES may be associated with better treatment response or higher wellbeing and LST or EOE with more negative outcomes.

Third, the samples in the current thesis were underpowered for genome-wide approaches and the findings should be considered exploratory and preliminary. Future studies should examine if the nominated genes and gene systems from the current study would be validated in larger, adequately powered samples. The success of the cross-trait polygenic score analysis could be utilised further to follow up on the biological mechanism underlying the variants that explained variations in environmental sensitivity in these analyses.

Fourth, one of the main limitation of the studies conducted here, and generally in the field, is that only additive rather than interactive genetic models are considered in genetic association studies. Future studies on the genetics of environmental sensitivity would benefit from examining its aetiology using genetic models that consider an interactive genetic/biological model, such as one recent model proposed by Moore and Depue (2016).

Fifth, the findings on cross-trait genetic correlations indicate that a significant proportion of the genetic factors of psychiatric disorders such as depression, anxiety and autism are correlated with those of environmental sensitivity. Since environmental sensitivity genes represent genetic influences that interact with various environmental contexts, they increase the risk for the development of a range of psychopathologies

whose development depend on environmental exposures. Therefore, identifying genes that reflect general sensitivity in addition to testing for main effects of genes for specific disorders could be a worthwhile new approach in psychiatric genetic research, than relying on detecting disease specific factors only.

Finally, in light of findings that genetically more sensitive individuals seem to benefit from their heightened sensitivity in certain contexts, such as in response to psychological therapies or over time in response to adversity, future research into what aspects of sensitivity facilitates positive adaptation is paramount in promoting/enhancing these factors in other people who are not naturally predisposed this way, as a function of their lesser general sensitivity. Relatedly, while much of the research in the field has studied GxE interactions in non-clinical samples, research is sparse on clinical populations. The GxE findings on major depression from Study 2 in Chapter 5 did not support the hypothesised differential susceptibility interaction model, emphasising the importance of considering the longitudinal effects of environmental sensitivity in its interaction with childhood risk factors in development of clinical disorders. Future research could examine whether and how environmental sensitivity may relate to higher or lower risk of clinical disorders in its interaction with high risk environmental exposures in childhood.

6.5 Conclusions

The research conducted in this thesis aimed to investigate the genetic basis of environmental sensitivity, a trait proposed to have a genetic basis according to differential susceptibility theories. This aim was examined using a variety of analytical approaches, including twin design to estimate the heritability of environmental sensitivity, candidate and genome-wide molecular approaches to identify genetic variants, genes and gene-systems associated with environmental sensitivity, and longitudinal GxE approaches to investigate its moderating effects on mental health and response to psychological therapies. The findings suggest that environmental sensitivity is heritable, that it shares some of its genetic influences with other phenotypes such as neuroticism, extraversion, depression, and anxiety. In addition, environmental sensitivity was found to act as a risk factor for the development of mental health problems in response to recent/concurrent adverse environmental exposures, but as a protective factor over time. Environmental sensitivity was also found to moderate the response to CBT treatment for anxiety disorders, with more sensitive individuals showing preferential response to individual CBT. In sum, genetic factors play an

important role in the aetiology of environmental sensitivity, but more research is needed to identify the molecular genetic factors underlying individual differences in this phenotype and their moderating effects on mental health and disorder.

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Appendices

Appendices Chapter 2

Appendix 2.1 The Highly Sensitive Person scale (HSP; Aron & Aron, 1997) – adult version

1.Are you easily overwhelmed by strong sensory input?
2.Do you seem to be aware of subtleties in your environment?
3.Do other people's moods affect you?
4.Do you tend to be more sensitive to pain?
5.Do you find yourself needing to withdraw during busy days, into bed or into a darkened room or any place where you can have some privacy and relief from stimulation?
6.Are you particularly sensitive to the effects of caffeine?
7.Are you easily overwhelmed by things like bright lights, strong smells, coarse fabrics, or sirens close by?
8.Do you have a rich, complex inner life?
9.Are you made uncomfortable by loud noises?
10.Are you deeply moved by the arts or music?
11.Does your nervous system sometimes feel so frazzled that you just have to go off by yourself?
12.Are you conscientious?
13.Do you startle easily?
14.Do you get rattled when you have a lot to do in a short amount of time?
15.When people are uncomfortable in a physical environment do you tend to know what needs to be done to make it more comfortable (like changing the lighting or the seating)?
16.Are you annoyed when people try to get you to do too many things at once?
17.Do you try hard to avoid making mistakes or forgetting things?
18.Do you make a point to avoid violent movies and TV shows?
19.Do you become unpleasantly aroused when a lot is going on around you?
20.Does being very hungry create a strong reaction in you, disrupting your concentration or mood?
21.Do changes in your life shake you up?
22.Do you notice and enjoy delicate or fine scents, tastes, sounds, works of art?
23.Do you find it unpleasant to have a lot going on at once?
24.Do you make it a high priority to arrange your life to avoid upsetting or overwhelming situations?
25.Are you bothered by intense stimuli, like loud noises or chaotic scenes?
26.When you must compete or be observed while performing a task, do you become so nervous or shaky that you do much worse than you would otherwise?
27.When you were a child, did parents or teachers seem to see you as sensitive or shy?

Appendix 2.2 Questionnaire items measuring the 38-item Highly Sensitive Child scale (HSC-38)

The unpublished Highly Sensitive Child Scale with 38 items (HSC-38) has been developed based on the Highly Sensitive Person scale (HSP; Aron & Aron, 1997) in order to measure sensory-processing sensitivity in Dutch school-aged children. The following five adaptations were made to the original HSP-scale:

1. Rather than 'Do you…' or 'Are you…', items were rephrased as 'I am…' or 'I find…'.
2. Difficult words that are likely to be unknown to children were replaced with simpler words. For example, 'Are you conscientious?' was changed into 'I am very precise'.
3. Single items that concerned an evaluation of two or more issues were divided into two or more separate items. For example, the original question from the HSP-scale 'Do you try hard to avoid making mistakes or forgetting things' was changed into 'I try not to forget things' (item 25) and 'I try not to make mistakes' (item 36).
4. The original item 'Are you particularly sensitive to the effects of caffeine?' was changed into 'Drinking coke, makes me feel uncomfortable', because most children below the age of 13 do not drink coffee, but may drink coke which sometimes causes effects similar to coffee.
5. The original item 'When you were a child, did parents or teachers seem to see you as sensitive or shy' was changed into 'My parents think I am sensitive' (item 26) and 'My teacher thinks I am shy' (item 3).

As a result of these adaptations the original HSP-scale that consisted of 27 items was changed into the HSC-38 scale consisting of 38 items.

Highly Sensitive Child (HSC-38) items - Study 1

1. I find it unpleasant to have a lot going on at once
2. I don't like unpleasant smells
3. My teacher thinks I am shy
4. I love nice sounds
5. I startle easily
6. I don't like bright lights
7. When I am hungry, I get in a bad mood
8. I love nice paintings
9. Drinking coke, makes me feel uncomfortable
10. Some music can make me really happy
11. When someone is happy, that makes me feel happy too
12. I love nice tastes
13. I don't like it when it is a mess around me
14. Some music can me make sad
15. Loud noises make me feel uncomfortable
16. I am annoyed when people try to get me to do too many things at once
17. I tend to feel pain easily
18. I notice it when small things have changed in my environment
19. When someone is sad, that makes me feel sad too
20. When I am hungry, I cannot think properly

21. I don’t like clothes that feel funny
22. I get nervous when I have to do a lot in little time
23. When someone is angry, that makes me feel angry too
24. I love nice smells
25. I try not to forget things
26. My parents think I am sensitive
27. I find it unpleasant to have a lot going on at once
28. I don’t like watching TV programs that have a lot of violence in them
29. I always think long and deep about everything
30. I try to avoid situations that I don’t like
31. When someone feels uncomfortable, I know what to do to change that
32. I don’t like loud noises
33. I don’t like it when things change in my life
34. When there is a lot going on around me, I prefer to be alone in a room
35. I don’t like watching movies that have a lot of violence in them
36. I try not to make mistakes
37. I am very precise
38. When someone observes me, I get nervous. This makes me perform worse than normal

Appendix 2.3 Results of principal component analyses of HSC-38 scale (Study 1)

Table 2.3.1 PCA on HSC-38; *selection method: Eigenvalues >1*

Component	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	9.76	25.69	25.69	4.10	10.78	10.78
2	3.59	9.44	35.13	3.00	7.91	18.68
3	2.18	5.74	40.87	2.82	7.42	26.10
4	1.79	4.71	45.57	2.68	7.05	33.15
5	1.40	3.67	49.24	2.63	6.93	40.08
6	1.33	3.50	52.74	2.60	6.83	46.92
7	1.16	3.06	55.80	2.24	5.89	52.81
8	1.12	2.94	58.74	1.98	5.21	58.02
9	1.09	2.87	61.62	1.37	3.60	61.62
10	0.97	2.55	64.17			
11	0.91	2.39	66.56			
12	0.89	2.34	68.89			
13	0.85	2.23	71.12			
14	0.73	1.92	73.04			
15	0.70	1.84	74.88			
16	0.69	1.81	76.69			
17	0.64	1.68	78.37			
18	0.63	1.65	80.02			
19	0.59	1.55	81.57			
20	0.57	1.50	83.07			
21	0.54	1.41	84.48			
22	0.52	1.37	85.85			
23	0.50	1.33	87.17			
24	0.47	1.23	88.40			
25	0.45	1.19	89.59			
26	0.44	1.16	90.76			
27	0.43	1.13	91.88			
28	0.38	1.01	92.89			
29	0.37	0.97	93.86			
30	0.36	0.94	94.79			
31	0.30	0.79	95.58			
32	0.29	0.77	96.35			
33	0.28	0.73	97.08			
34	0.26	0.68	97.76			
35	0.25	0.67	98.43			
36	0.24	0.63	99.06			
37	0.20	0.52	99.58			
38	0.16	0.43	100.00			

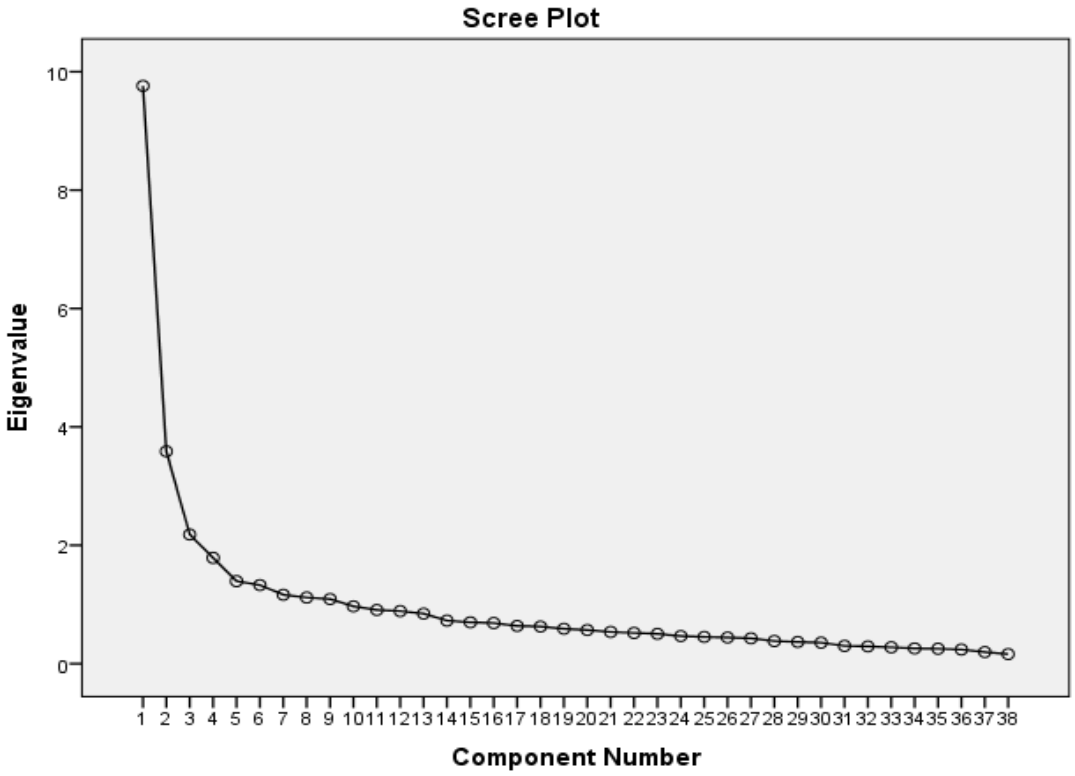

Figure 2.3.1 Scree plot of the principal components of the HSC-38

Table 2.3.2 PCA on HSC-38; *selection method: 3 principle components* (Study 1)

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	9.76	25.69	25.69	9.76	25.69	25.69	6.29	16.55	16.55
2	3.59	9.44	35.13	3.59	9.44	35.13	5.22	13.73	30.28
3	2.18	5.74	40.87	2.18	5.74	40.87	4.02	10.58	40.87
4	1.79	4.71	45.57						
5	1.40	3.67	49.24						
6	1.33	3.50	52.74						
7	1.16	3.06	55.80						
8	1.12	2.94	58.74						
9	1.09	2.87	61.62						
10	0.97	2.55	64.17						
11	0.91	2.39	66.56						
12	0.89	2.34	68.89						
13	0.85	2.23	71.12						
14	0.73	1.92	73.04						
15	0.70	1.84	74.88						
16	0.69	1.81	76.69						
17	0.64	1.68	78.37						
18	0.63	1.65	80.02						
19	0.59	1.55	81.57						
20	0.57	1.50	83.07						
21	0.54	1.41	84.48						
22	0.52	1.37	85.85						
23	0.50	1.33	87.17						
24	0.47	1.23	88.40						
25	0.45	1.19	89.59						
26	0.44	1.16	90.76						
27	0.43	1.13	91.88						
28	0.38	1.01	92.89						
29	0.37	0.97	93.86						
30	0.36	0.94	94.79						
31	0.30	0.79	95.58						
32	0.29	0.77	96.35						
33	0.28	0.73	97.08						
34	0.26	0.68	97.76						
35	0.25	0.67	98.43						
36	0.24	0.63	99.06						
37	0.20	0.52	99.58						
38	0.16	0.43	100.00						

Table 2.3.3 HSC-38 rotated component matrix. 12 selected items are highlighted (Study 1)

		1	2	3
1	I find it unpleasant to have a lot going on at once	.104	**.567**	-.044
2	I don't like unpleasant smells	.341	.297	-.222
3	My teacher thinks I am shy	-.113	.371	.242
4	I love nice sounds	.661	.115	.024
5	I startle easily	.049	.489	.258
6	I don't like bright lights	.010	.459	.286
7	When I am hungry, I get in a bad mood	.003	.584	.141
8	I love nice paintings	.603	.112	.243
9	Drinking coke, makes me feel uncomfortable	-.083	.257	.460
10	Some music can make me really happy	**.674**	.088	-.065
11	When someone is happy, that makes me feel happy too	.682	-.035	.123
12	I love nice tastes	**.739**	.172	-.148
13	I don't like it when it is a mess around me	.536	.167	.187
14	Some music can me make sad	.354	.105	.487
15	Loud noises make me feel uncomfortable	.125	.425	**.376**
16	I am annoyed when people try to get me to do too many things at once	.308	**.597**	-.085
17	I tend to feel pain easily	-.013	.615	.344
18	I notice it when small things have changed in my environment	**.431**	.204	.236
19	When someone is sad, that makes me feel sad too	.433	.193	.469
20	When I am hungry, I cannot think properly	.114	.656	.078
21	I don't like clothes that feel funny	.432	.450	.023
22	I get nervous when I have to do a lot in little time	.335	**.580**	.187
23	When someone is angry, that makes me feel angry too	.092	.388	.418
24	I love nice smells	**.754**	.166	-.006
25	I try not to forget things	.682	.096	.026
26	My parents think I am sensitive	.182	.271	.374
27	I find it unpleasant to have a lot going on at once	.236	.697	.060
28	I don't like watching TV programs that have a lot of violence in them	.006	.141	**.688**
29	I always think long and deep about everything	.397	.157	.524
30	I try to avoid situations that I don't like	.558	.141	.239
31	When someone feels uncomfortable, I know what to do to change that	.547	-.066	.362
32	I don't like loud noises	.165	.266	**.480**
33	I don't like it when things change in my life	.289	**.483**	.317
34	When there is a lot going on around me, I prefer to be alone in a room	.170	.544	.332
35	I don't like watching movies that have a lot of violence in them	.045	.140	.762
36	I try not to make mistakes	.623	.110	.200
37	I am very precise	.472	-.036	.451
38	When someone observes me, I get nervous. This makes me perform worse than normal	.124	**.546**	.232

Appendix 2.4 Results of confirmatory factor analysis of the 12- item HSC scale (Study 1)

Table 2.4.1 CFA parameters of the 3-factor model (Study1)

Latent variables and item content	Estimate	Std.Err
EOE		
Unpleasant a lot going on	0.658	0.124
Annoyed when too many things	1.014	0.112
Nervous when a lot to do	1.244	0.104
Don't like changes	1.020	0.109
Nervous when observed	1.026	0.121
AES		
Music makes me happy	1.038	0.104
Love nice tastes	1.304	0.105
Notice small changes	0.615	0.106
Love nice smells	1.299	0.114
LST		
Loud noises make me uncomfortable	1.488	0.117
Don't like violence in TV	0.832	0.157
Don't like loud noises	1.487	0.125

Table 2.4.2 Covariance matrix among latent variables of the 3-factor model (Study 1)

	EOE	AES	LST
EOE		.570	.613
AES			.234
LST			

Table 2.4.3 CFA parameters of the bi-factor model (Study 1)

Latent variables and items content	Estimate	Std. Err
EOE		
Unpleasant a lot going on	1.000	
Annoyed when too many things	-0.029	0.162
Nervous when a lot to do	-0.363	0.157
Don't like changes	-0.056	0.154
Nervous when observed	-0.230	0.171
AES		
Music makes me happy	1.000	
Love nice tastes	1.208	0.116
Notice small changes	0.333	0.120
Love nice smells	1.028	0.114
LST		
Loud noises make me uncomfortable	1.000	
Don't like violence in TV	0.585	0.151
Item 32	1.664	0.112
HSC – General factor		
Unpleasant a lot going on	1.000	
Annoyed when too many things	1.046	0.116
Nervous when a lot to do	1.315	0.112
Don't like changes	1.031	0.120
Nervous when observed	1.046	0.125
Music makes me happy	0.461	0.126
Love nice tastes	0.642	0.122
Notice small changes	0.592	0.144
Love nice smells	0.779	0.126
Loud noises make me uncomfortable	0.950	0.123
Don't like violence in TV	0.628	0.157
Don't like loud noises	0.787	0.144

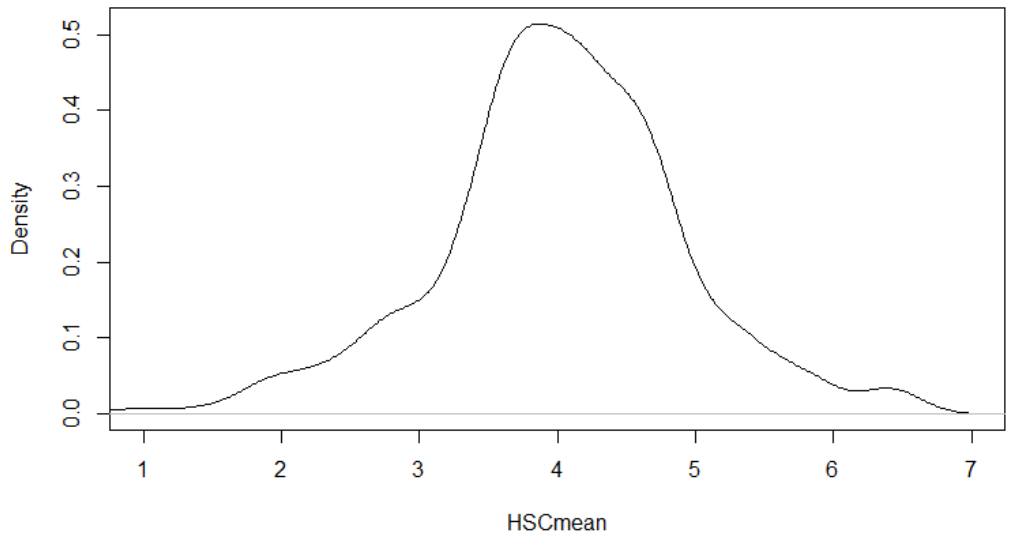

Figure 2.4.1 Density plot to illustrate the distribution of the 12-item HSC scale (Study1)

Appendix 2.5 Results of divergent validity analysis (Study 1)

Table 2.5.1 Heterotrait-monotrait ratio of correlations (Study 1)

	HSC	HSC-EOE	HSC-AES	HSC-LST
HSC				
HSC-EOE	.932			
HSC-AES	.748	.589		
HSC-LST	.701	.661	.246	
BAS	.511	.386	.620	.180
BIS	.690	.649	.504	.490
PE	.390	.272	.470	.181
NE	.431	.362	.328	.316
EC	.424	.360	.392	.258
PA	.310	.139	.503	.117
NA	.244	.207	.200	.3183

HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensitivity Threshold; BIS = Behavioural Inhibition System; BAS = Behavioural Activation System; EC = Effortful Control; NE = Negative Emotionality; PE = Positive Emotionality

Appendix 2.6 Results of confirmatory factor analysis of the 12-item HSC scale (Study 2)

Table 2.6.1 CFA parameters of the 3-factor model (Study 2)

Latent variables and items content	Estimate	Std.Err
EOE		
Unpleasant a lot going on	.914	0.130
Annoyed when too many things	1.230	0.155
Nervous when a lot to do	1.183	0.157
Don't like changes	0.717	0.160
Nervous when observed	0.904	0.155
AES		
Music makes me happy	0.953	0.131
Love nice tastes	0.840	0.126
Notice small changes	0.531	0.131
Love nice smells	1.059	0.147
LST		
Loud noises make me uncomfortable	1.614	0.178
Don't like violence in TV	0.711	0.160
Don't like loud noises	1.900	0.179

Table 2.6.2 Covariance matrix of latent variables (Study 2)

	EOE	AES	LST
EOE		.448	.480
AES			.153
LST			

Table 2.6.3 CFA parameters of the bi-factor model (Study 2)

Latent variables and items content	Estimate	Std.Err
EOE		
Unpleasant a lot going on	1.000	
Annoyed when too many things	.057	.210
Nervous when a lot to do	-0.489	.240
Notice small changes	0.285	.180
Nervous when observed	-0.030	.202
AES		
Music makes me happy	1.000	
Love nice tastes	0.883	0.138
Notice small changes	0.444	0.135
Love nice smells	0.882	0.153
LST		
Loud noises make me uncomfortable	1.000	
Don't like violence in TV	0.551	.143
Don't like loud noises	1.968	.072
HSC – General factor		
Unpleasant a lot going on	1.000	
Annoyed when too many things	1.178	0.153
Nervous when a lot to do	1.343	0.176
Don't like changes	0.666	0.153
Nervous when observed	0.915	0.151
Music makes me happy	0.421	0.125
Love nice tastes	0.244	0.092
Notice small changes	0.300	0.160
Love nice smells	0.536	0.131
Loud noises make me uncomfortable	0.927	0.163
Don't like violence in TV	0.420	0.166
Don't like loud noises	0.845	0.157

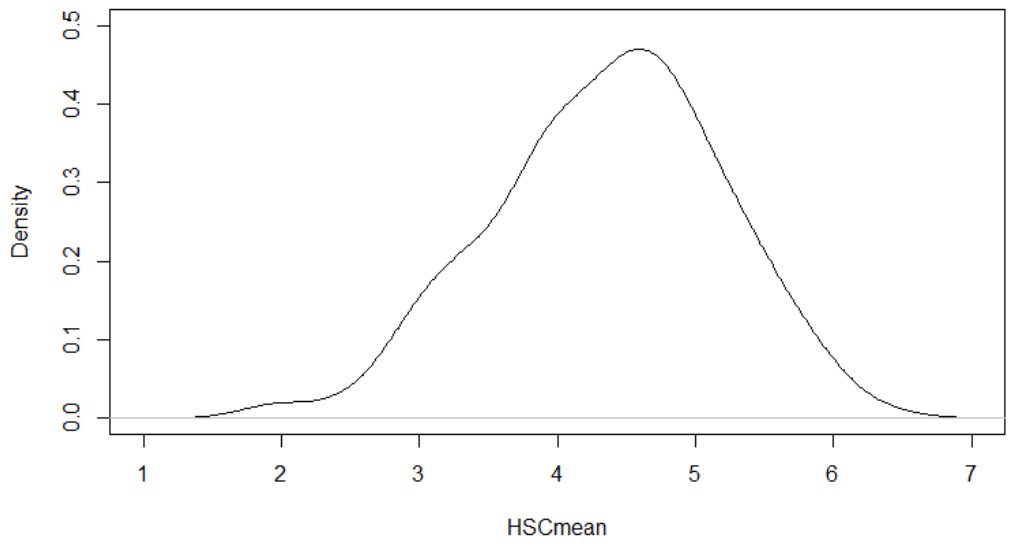

Figure 2.6.1 Density plot to illustrate the distribution of the 12-item HSC scale (Study 2)

Appendix 2.7 Results of divergent validity analysis (Study 2)

Table 2.7.1 Heterotrait-monotrait ratio of correlations (Study 2)

	HSC	HSC_EOE	HSC_AES	HSC-LST
HSC				
HSC-EOE	.903			
HSC-AES	.774	.600		
HSC-LST	.681	.536	.309	
BAS	.402	.331	.487	.117
BIS	.527	.528	.366	.334
PE	.658	.490	.712	.354
NE	.666	.680	.443	.420
EC	.646	.544	.608	.364

HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensitivity Threshold; BIS = Behavioural Inhibition System; BAS = Behavioural Activation System; EC = Effortful Control

Appendix 2.8 Results of confirmatory factor analysis of the 12-item HSC scale (Study 4)

Table 2.8.1 CFA parameters of the 3-factor model (Study 4)

Latent variables and items content	Estimate	Std.Err
EOE		
Unpleasant a lot going on	1.330	0.039
Annoyed when too many things	1.278	0.042
Nervous when a lot to do	1.254	0.045
Don't like changes	1.106	0.044
Nervous when observed	1.228	0.046
AES		
Music makes me happy	0.692	0.047
Love nice tastes	1.100	0.043
Notice small changes	0.416	0.049
Love nice smells	1.073	0.041
LST		
Loud noises make me uncomfortable	1.400	0.042
Don't like violence in TV	0.664	0.055
Don't like loud noises	1.543	0.042

Table 2.8.2 Covariance matrix of latent variables (Study 4)

	EOE	AES	LST
EOE		.296	.637
AES			.136
LST			

Table 2.8.3 CFA parameters of the bi-factor model (Study 4)

Latent variables and items content	Estimate	Std.Err
EOE		
Unpleasant a lot going on	1.000	
Annoyed when too many things	1.168	0.057
Nervous when a lot to do	0.912	0.068
Don't like changes	0.549	0.068
Nervous when observed	0.657	0.081
AES		
Music makes me happy	1.000	
Love nice tastes	1.183	0.047
Notice small changes	0.360	0.051
Love nice smells	1.127	0.044
LST		
Loud noises make me uncomfortable	1.000	
Don't like violence in TV	-0.241	0.102
Don't like loud noises	0.512	0.121
HSC – General factor		
Unpleasant a lot going on	1.000	
Annoyed when too many things	0.769	0.049
Nervous when a lot to do	0.883	0.052
Don't like changes	0.992	0.055
Nervous when observed	1.049	0.059
Music makes me happy	0.186	0.041
Love nice tastes	0.163	0.044
Notice small changes	0.422	0.051
Love nice smells	0.227	0.047
Loud noises make me uncomfortable	1.257	0.067
Don't like violence in TV	0.862	0.067
Don't like loud noises	1.338	0.057

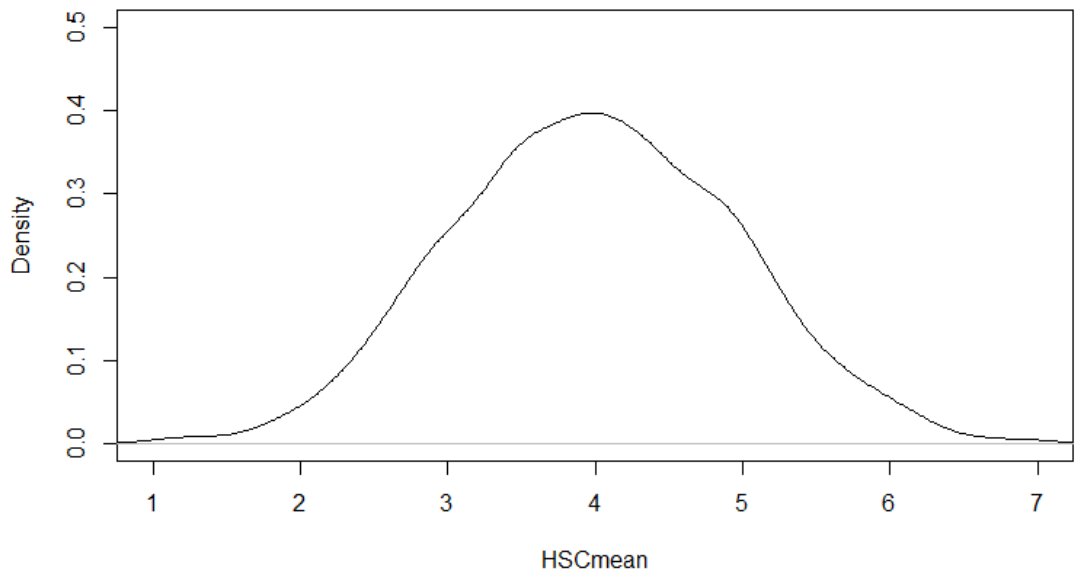

Figure 2.8.1 Density plot to illustrate the distribution of the 12-item HSC scale (Study 4)

Appendix 2.9 Results of divergent validity analysis (Study 4)

Table 2.9.1 Heterotrait-monotrait ratio of correlations (Study 4)

	HSC	HSC-EOE	HSC-AES	HSC-LST
HSC				
HSC-EOE	.893			
HSC-AES	.581	.317		
HSC-LST	.763	.684	.192	
Neuroticism	.449	.484	.142	.333
Extraversion	.439	.368	.285	.343
Openness	.341	.205	.372	.235
Agreeableness	.249	.179	.191	.210
Conscientiousness	.234	.197	.213	.117

HSC = Highly Sensitive Child Scale; HSC-EOE = Ease of Excitation; HSC-AES = Aesthetic Sensitivity; HSC-LST = Low Sensitivity Threshold

Appendices Chapter 3

Appendix 3.1 Results of the univariate ACE analyses

Table 3.1 ACE estimates from sex limitation models for HSC and its three components

		Variance Components					
		A		C		E	
		male	female	male	female	male	female
HSC	Qualitative, r_g= free	.53 (.25, .61)	.37 (.11, .52)	.00 (.00, .23)	.07 (.00, .30)	.47 (.39, .58)	.55 (.48, .64)
	Qualitative, r_c= free	.53 (.25, .61)	.38 (.11, .52)	.00 (.00, .23)	.00 (.00, .30)	.47 (.39, .58)	.55 (.48, .64)
	Quantitative, r_g= .5 & r_c=1	.53 (.26, .61)	.38 (.11, .52)	.00 (.00, .22)	.00 (.00, .30)	.47 (.39, 58)	.55 (.48, .64)
	Scalar	.48 (.31, -.53)		.00 (.00, -.13)		.52 (.47, -.59)	
	Homogeneity	.47 (.30, -.53)		.00 (.00, -.13)		.53 (.47, -.59)	
EOE	Qualitative, r_g= free	.29 (.00, .56)	.29 (.02, .48)	.20 (.00, .45)	.11 (.00, .34)	.52 (.42, .63)	.60 (.52, .69)
	Qualitative, r_c= free	.27 (.00, .55)	.26 (.00, .47)	.21 (.00, .45)	.14 (.00, .37)	.52 (.42, .64)	.60 (.52, .70)
	Quantitative, r_g= .5 & r_c=1	.29 (.00, .57)	.41 (.00, .49)	.19 (.00, .46)	.01 (.00, .38)	.51 (.41, .65)	.59 (.51, .67)
	Scalar	42 (.24, -.49)		.00 (.00, -.14)		.57 (.51, -.64)	
	Homogeneity	.42 (.23, -.48)		.01 (.00, -.14)		.58 (.52, -.65)	
AES	Qualitative, r_g= free	.36 (.21 ,.47)	.35 (.07, .45)	.00 (.00, .10)	.01 (.00, .24)	.64 (.53, .75)	.63 (.55, .73)
	Qualitative, r_c= free	.36 (.21, .46)	.32 (.08, .44)	.00 (.00, .11)	.04 (.00, .23)	.64 (.53, .75)	.64 (.56, .73)
	Quantitative, r_g= .5 & r_c=1	.36 (.21, .46)	.32 (.08, .43)	.00 (.00, .11)	.04 (.00, .23)	.64 (.54, .75)	.64 (.56, .73)
	Scalar	.36 (.25, .42)		.00 (.00, .07)		.64 (.58, .71)	
	Homogeneity	.36 (.26, .42)		.00 (.00, .06)		.64 (.58, .71)	

LST	Qualitative, r_g= free	.45 (.15, .57)	.29 (.01, .46)	.03 (.00, .28)	.10 (.00, .34)	.52 (.43, .63)	.61 (.53, .70)
	Qualitative, r_c= free	.45 (.15, .57)	.29 (.01, .46)	.03 (.00, .28)	.10 (.00, .34)	.52 (.43, .63)	.61 (.53, .70)
	Quantitative, r_g= .5 & r_c=1	.46 (.15, .57)	.29 (.01, .46)	.03 (.00, .28)	.10 (.00, .34)	.52 (.43, .63)	.61 (.53, .70)
	Scalar	.41 (.27-.47)		.00 (.00-.00)		.59 (.53-.65)	
	Homogeneity	.41 (.26-.47)		.00 (.00-.11)		.59 (.53-.66)	

Qualitative ACE (r_g=Free) and Qualitative ACE (r_c=Free) = models that allow differences in source of variation in males and females, where either r_c or r_g is free to be estimated for opposite sex twin pairs and can vary below the values assigned to same-sex dizygotic pairs; Quantitative ACE =model that allows differences in the extent of influence of ACE parameters in males and females, with r_c and r_g in opposite sex twins being fixed to 1 and .5 respectively, estimating the ACE parameters from same sex twin pairs only; Scalar = model with no sex differences in ACE parameters but scalar term on males; Homogeneity= univariate ACE model with no difference between males and females

Table 3.2 Univariate model fit results for personality, anxiety, and depression

		Model fit			Compared to fully saturated model		
		-2ll	df	AIC	Δ -2ll	Δ df	*p*
Neuroticism	Fully saturated	6559.76	1131	4297.76			
	Constrained	6582.64	1147	4288.64	22.89	16	0.12
	ACE	6583.84	1152	4279.84	24.09	21	0.29
Openness	Fully saturated	6207.96	1129	3949.96			
	Constrained	6224.07	1145	3934.07	16.11	16	0.45
	ACE	6233.20	1150	3933.20	25.24	21	0.24
Conscientiousness	Fully saturated	6270.45	1125	4020.45			
	Constrained	6289.14	1141	4007.14	18.68	16	0.29
	ACE	6298.06	1146	4006.06	27.61	21	0.15
Extraversion	Fully saturated	6389.55	1129	4131.55			
	Constrained	6406.31	1145	4116.31	16.76	16	0.4
	ACE	6421.47	1150	4121.47	31.93	21	0.06
Agreeableness	Fully saturated	6208.85	1127	3954.85			
	Constrained	6239.35	1143	3953.35	30.49	16	0.02
	ACE	6243.96	1148	3947.96	35.11	21	0.03
Depression	Fully saturated	17586.99	2865	11856.99			
	Constrained	17605.05	2881	11843.05	18.05	16	0.32
	ACE	17731.61	2886	11959.61	144.62	21	< .001

Anxiety	Fully saturated	18543.07	2865	12813.07			
	Constrained	18571.54	2881	12809.54	28.47	16	0.03
	ACE	18665.92	2886	12893.92	122.85	21	<.001

Fully saturated model=model with maximum number of parameters describing the data; Constrained = sub-model of the fully saturated model, testing the assumptions of twin design, with means and variances equated across twins and zygosity; −2ll= minus twice the log likelihood; df= degrees of freedom; AIC= Akaike's information criterion; Δ -2ll =difference in -2ll value; Δ df= difference in degrees of freedom; *p*= *p*-value.

Appendix 3.2 Results the multivariate ACE analyses, Cholesky decomposition correlated factors model

Table 3.3 Results of the Cholesky decomposition correlated factors model

	rA	rC	rE	rph	phA	phC	phE
EOE - AES	0.45 (.23,.67)	1	0.14 (.07,.22)	0.27 (.23,.30)	0.17 (.07,.24)	0.01 (-.03,.08)	0.09 (.04,.14)
EOE - LST	0.62 (.43,.78)	1	0.45 (.39,.51)	0.52 (.49,.55)	0.25 (.12,.32)	0.01 (-.03,.08)	0.26 (.22,.32)
AES - LST	0.34 (.14,.56)	1	0.06 (-.01,.13)	0.17 (.13,.21)	0.13 (.04,.19)	0.01 (-.03,.08)	0.04 (-.01,.08)

rA=genetic correlation; rC=common environmental influences correlation; rE=non-shared environmental influences; rph= phenotypic correlation; phA=phenotypic correlation due to A; phC=phenotypic correlation due to C; phE=phenotypic correlation due to E.

Appendices Chapter 4

Appendix 4.1 Results of GWAS in TEDS and CogBIAS data

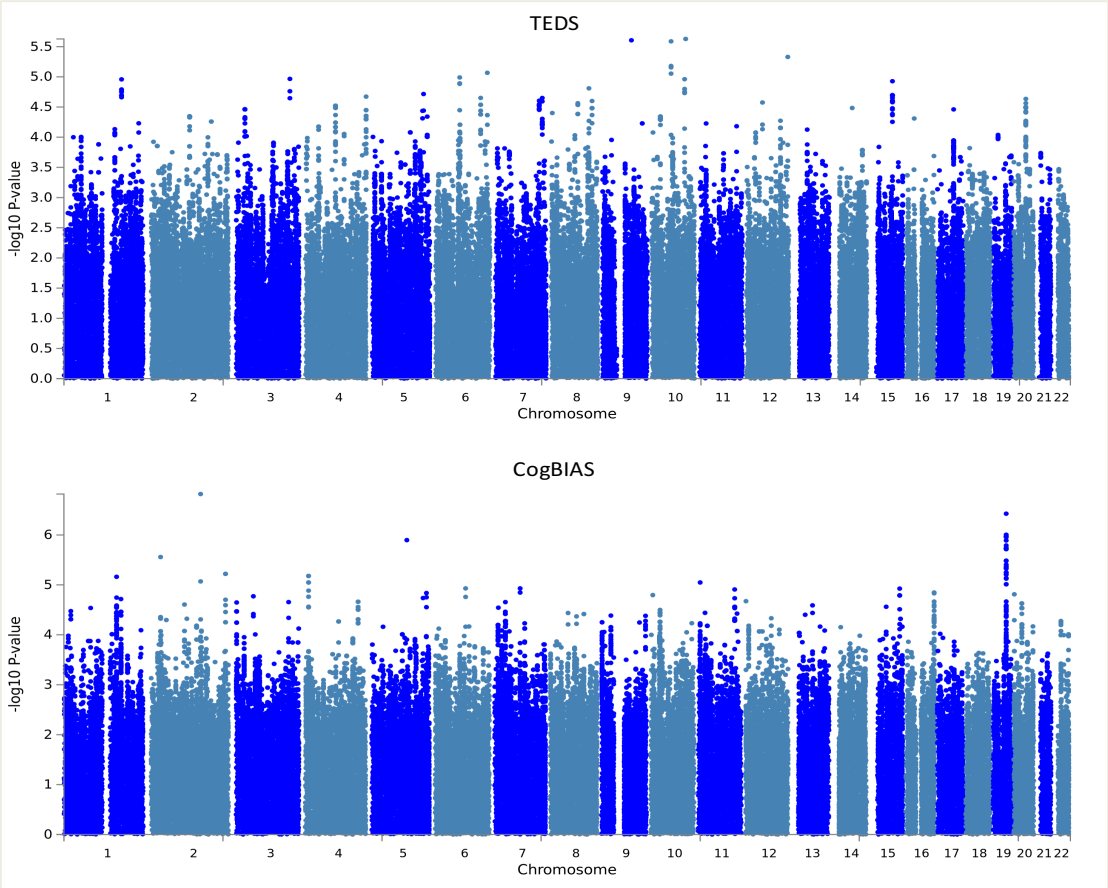

Figure 4.1 Manhattan Plots of TEDS and CogBIAS GWAS

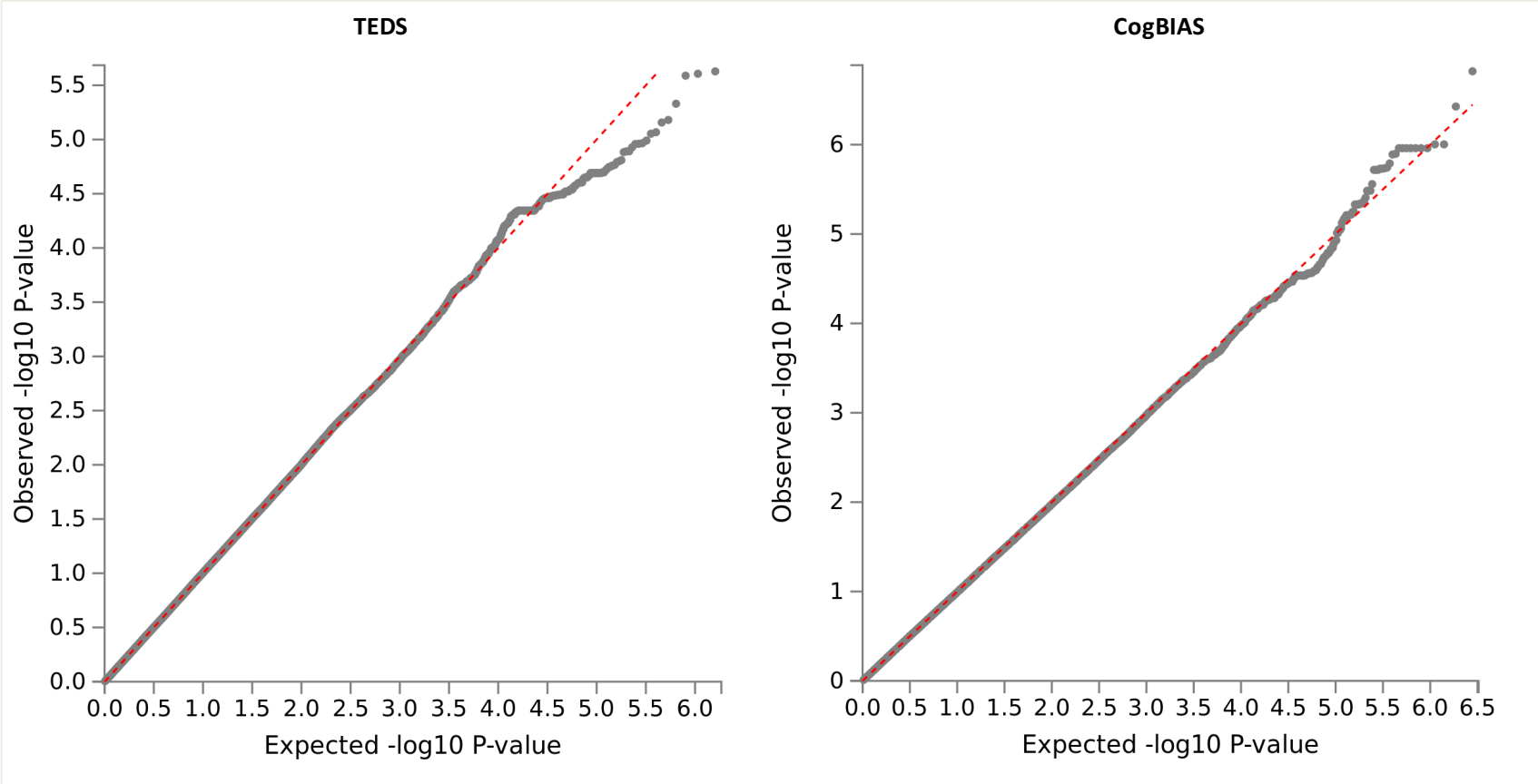

Figure 4.2 QQ plots of GWAS p-values in TEDS and CogBIAS

Table 4.1 Top 20 GWAS SNPs in TEDS and CogBIAS

Top 20 SNPs in TEDS data									The same SNPs in CogBIAS data				
CHR	SNP	BP	A1	BETA	SE	STAT	*P*	*P* (GC)	A1	BETA	SE	STAT	*P*
10	rs4918121	106392464	A	0.27	0.06	4.76	**2.4E-06**	2.4E-06	A	0.04	0.07	0.6	0.57
9	rs4262391	91189708	T	0.34	0.07	4.75	**2.5E-06**	2.5E-06	-	-	-	-	-
10	rs11006258	60538659	A	-0.26	0.05	-4.75	**2.6E-06**	2.7E-06	-	-	-	-	-
12	rs11060151	129615327	A	-0.32	0.07	-4.62	**4.7E-06**	4.8E-06	A	0.08	0.10	0.8	0.41
10	rs10509093	60523769	G	-0.25	0.05	-4.54	**6.6E-06**	6.8E-06	-	-	-	-	-
10	rs11006256	60525880	G	-0.24	0.05	-4.53	**7.0E-06**	7.2E-06	-	-	-	-	-
6	rs2096982	162660989	A	-0.23	0.05	-4.49	**8.6E-06**	8.8E-06	A	-0.08	0.06	-1.3	0.20
10	rs10826238	60527208	C	-0.24	0.05	-4.48	**8.8E-06**	9.1E-06	-	-	-	-	-
6	rs16886446	76012047	T	0.89	0.20	4.45	**1.0E-05**	1.1E-05	T	-0.02	0.06	-0.3	0.78
3	rs7636669	168674012	A	-0.36	0.08	-4.44	**1.1E-05**	1.1E-05	A	-0.04	0.09	-0.4	0.68
10	rs10883597	102999754	T	0.24	0.05	4.43	**1.1E-05**	1.1E-05	T	0.07	0.07	1.0	0.31
1	rs10797664	180988636	T	-0.25	0.06	-4.43	**1.1E-05**	1.1E-05	-	-	-	-	-
15	rs7498016	69802419	C	-0.35	0.08	-4.42	**1.2E-05**	1.2E-05	C	-0.04	0.09	-0.4	0.70
6	rs73463831	75918659	C	0.95	0.22	4.40	**1.3E-05**	1.3E-05	-	-	-	-	-
6	rs73463834	75918900	A	0.95	0.22	4.40	**1.3E-05**	1.3E-05	-	-	-	-	-
6	rs73463835	75918993	A	0.94	0.22	4.39	**1.3E-05**	1.3E-05	-	-	-	-	-
8	rs1160120	118641568	G	0.26	0.06	4.36	**1.6E-05**	1.6E-05	G	-0.01	0.07	-0.2	0.83
10	rs11190878	103009908	G	0.24	0.06	4.35	**1.6E-05**	1.6E-05	G	-0.09	0.07	-1.2	0.22
1	rs10910849	180980443	A	-0.24	0.05	-4.35	**1.6E-05**	1.7E-05	A	-0.02	0.06	-0.3	0.74
1	rs35672928	180969115	G	-0.24	0.05	-4.33	**1.7E-05**	1.8E-05	-	-	-	-	-

Top 20 SNPs in CogBIAS									The same SNPs in TEDS data				
CHR	SNP	BP	A1	BETA	SE	STAT	*P*	*P* (GC)	A1	BETA	SE	STAT	*P*
2	rs6435333	155560333	C	-0.56	0.10	-5.35	**1.5E-07**	1.7E-07	-	-	-	-	-
19	rs55811526	41450934	T	0.33	0.06	5.17	**3.7E-07**	4.1E-07	-	-	-	-	-
19	rs4062238	41451576	G	0.32	0.06	4.97	**9.9E-07**	1.1E-06	-	-	-	-	-
19	rs4560022	41451810	C	0.32	0.06	4.97	**9.9E-07**	1.1E-06	-	-	-	-	-
19	rs12972933	41455816	T	0.32	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
19	rs4239510	41453499	T	0.31	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
19	rs4239511	41453582	C	0.32	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
19	rs4322765	41458785	T	0.32	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
19	rs4560023	41451893	C	0.32	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
19	rs4803411	41463593	A	0.32	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
19	rs58436969	41462418	T	0.32	0.06	4.95	**1.1E-06**	1.2E-06	-	-	-	-	-
5	rs17517197	110357426	G	-0.54	0.11	-4.92	**1.3E-06**	1.4E-06	-	-	-	-	-
19	rs8110485	41448205	G	0.32	0.06	4.92	**1.3E-06**	1.4E-06	-	-	-	-	-
19	rs2099361	41498348	C	0.32	0.06	4.87	**1.6E-06**	1.7E-06	-	-	-	-	-
19	rs10417579	41465130	T	0.30	0.06	4.85	**1.8E-06**	1.9E-06	-	-	-	-	-
19	rs56317391	41477304	A	0.31	0.06	4.85	**1.8E-06**	2.0E-06	-	-	-	-	-
19	rs3889806	41459241	T	0.31	0.06	4.84	**1.9E-06**	2.0E-06	-	-	-	-	-
19	rs7251436	41452293	A	0.31	0.06	4.84	**1.9E-06**	2.0E-06	-	-	-	-	-
19	rs11673114	41465979	G	0.31	0.06	4.84	**1.9E-06**	2.1E-06	-	-	-	-	-
19	rs988900	41472213	A	0.31	0.06	4.84	**1.9E-06**	2.1E-06	-	-	-	-	-

Associations with $p < .05$ are in bold; Empty cells indicate the SNPs were not available in the respective data set

Appendix 4.2 Results of cross-trait polygenic score analyses in TEDS, CogBIAS and meta-analysed data sets

Figure 4.1 AGREEABLENESS

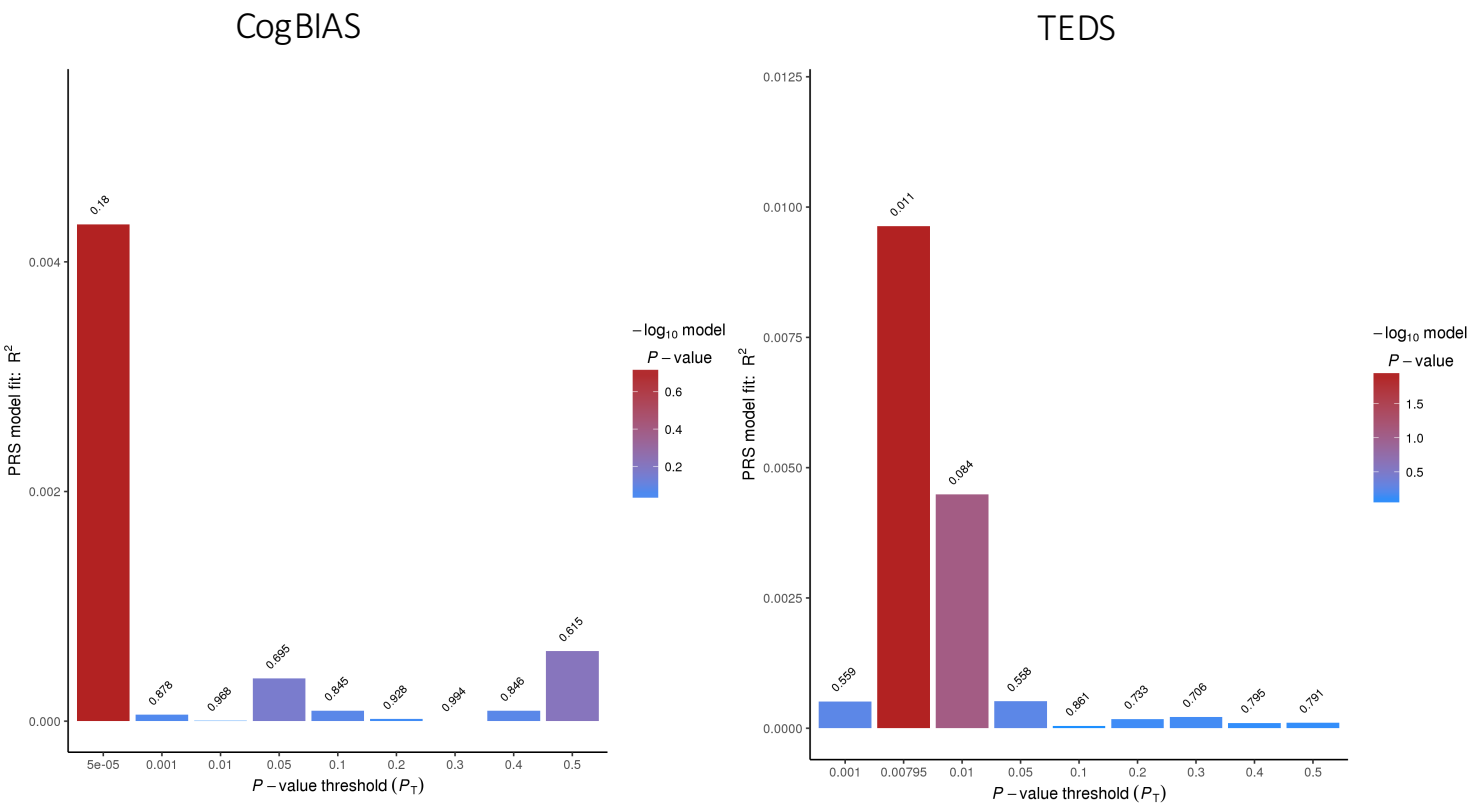

Figure 4.2 ANXIETY

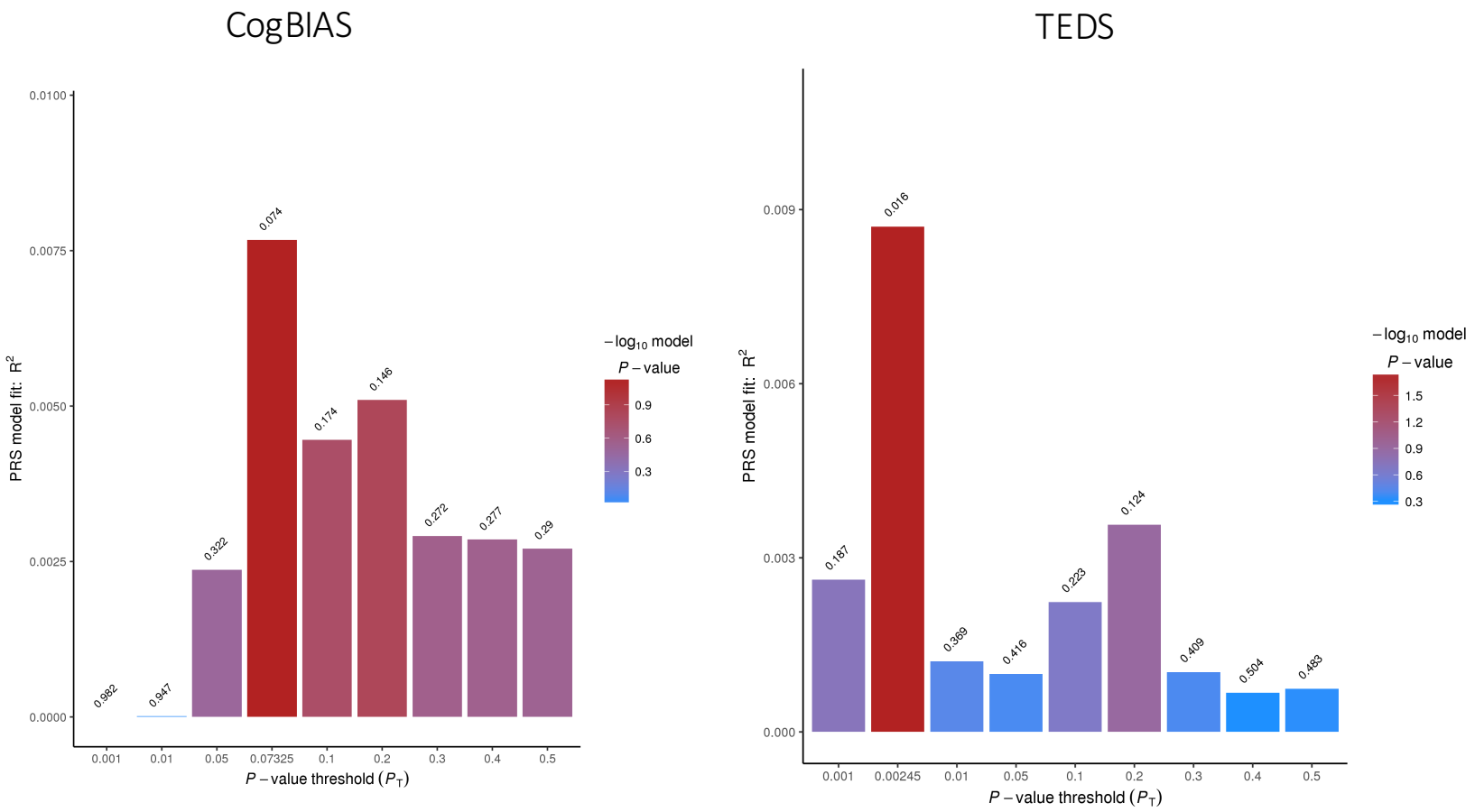

Figure 4.3 CONSCIENTIOUSNESS

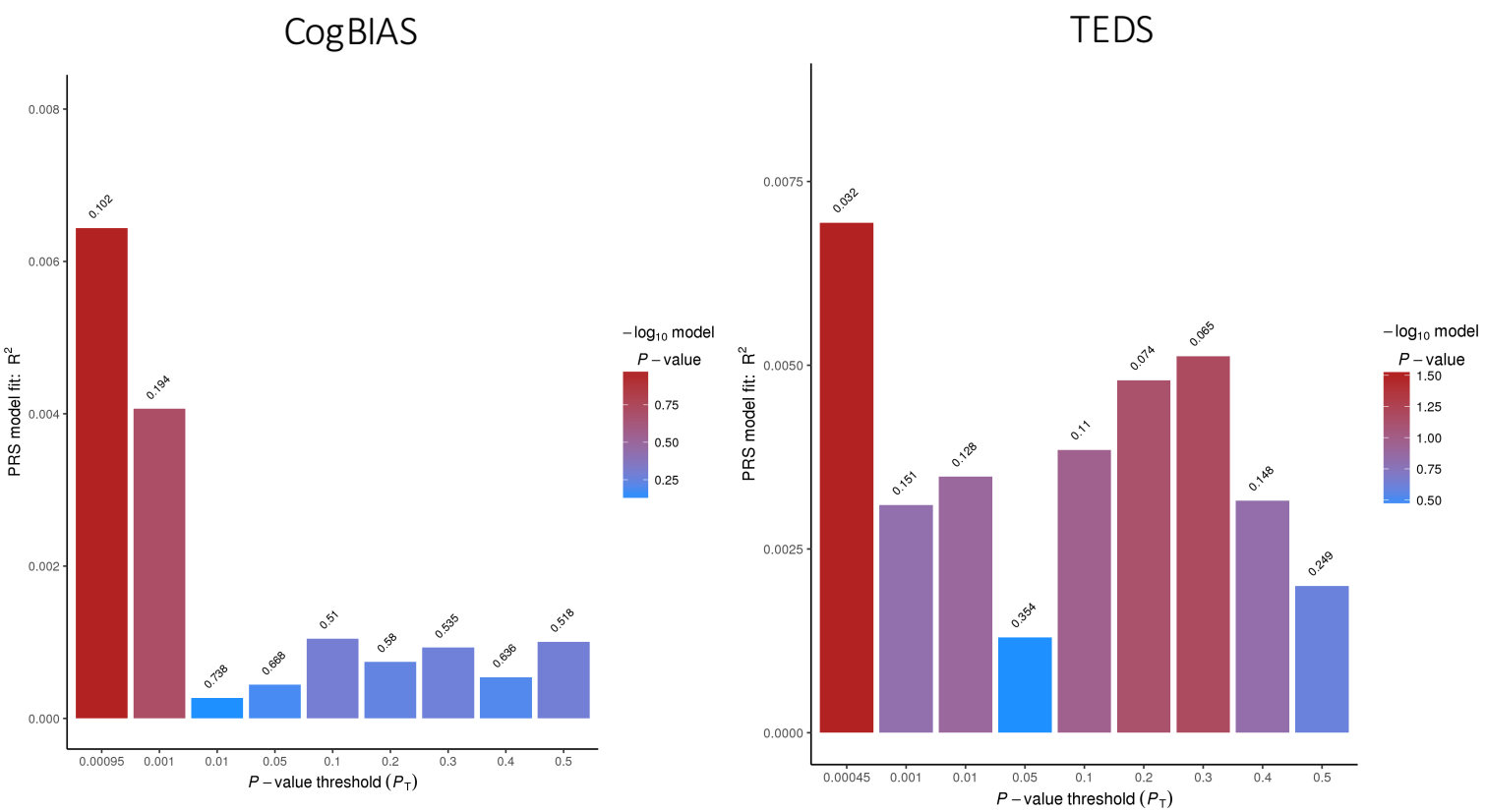

Figure 4.4 DEPRESSION

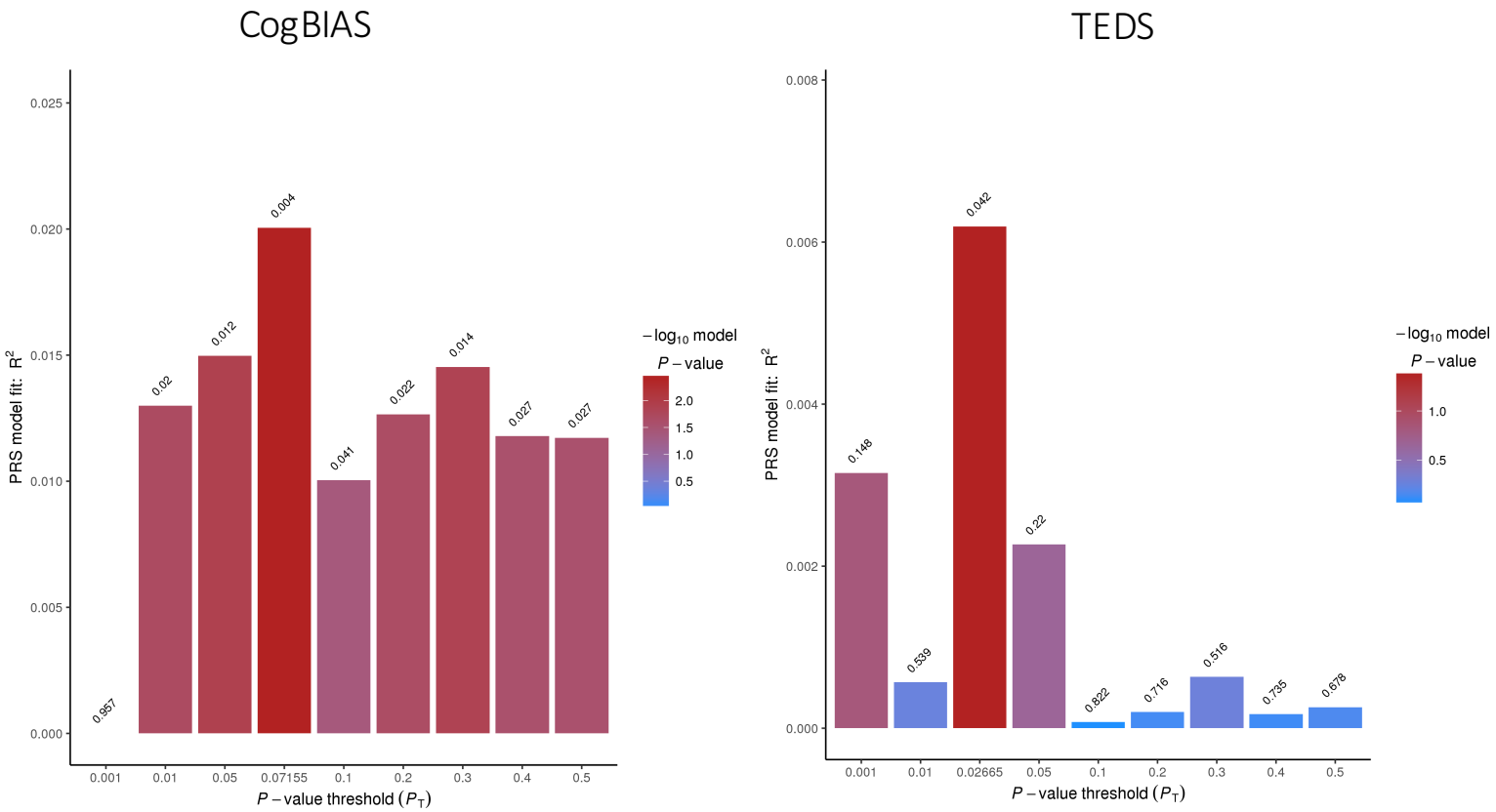

Figure 4.5 EDUCATIONAL ATTAINMENT

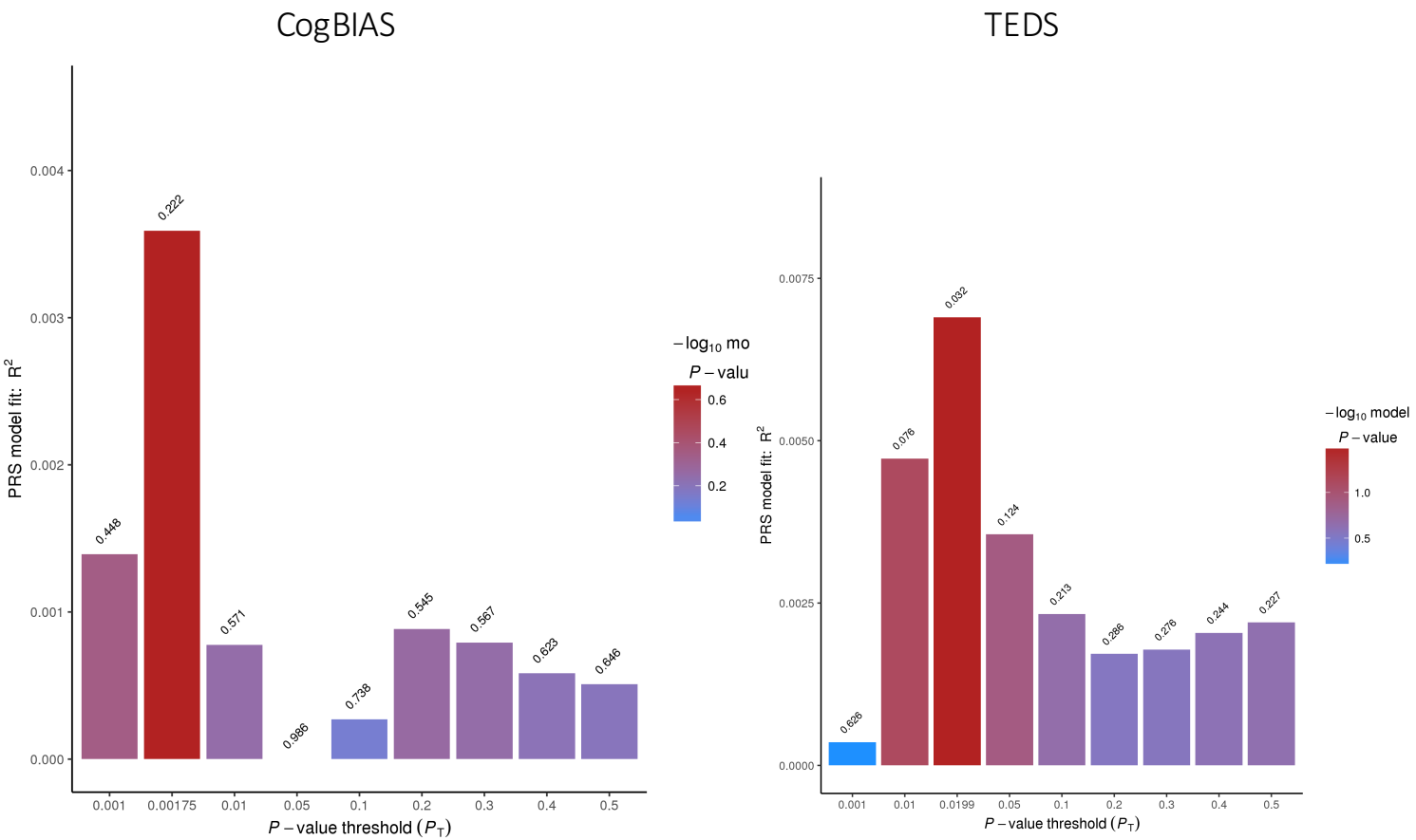

Figure 4.6 EXTRAVERSION

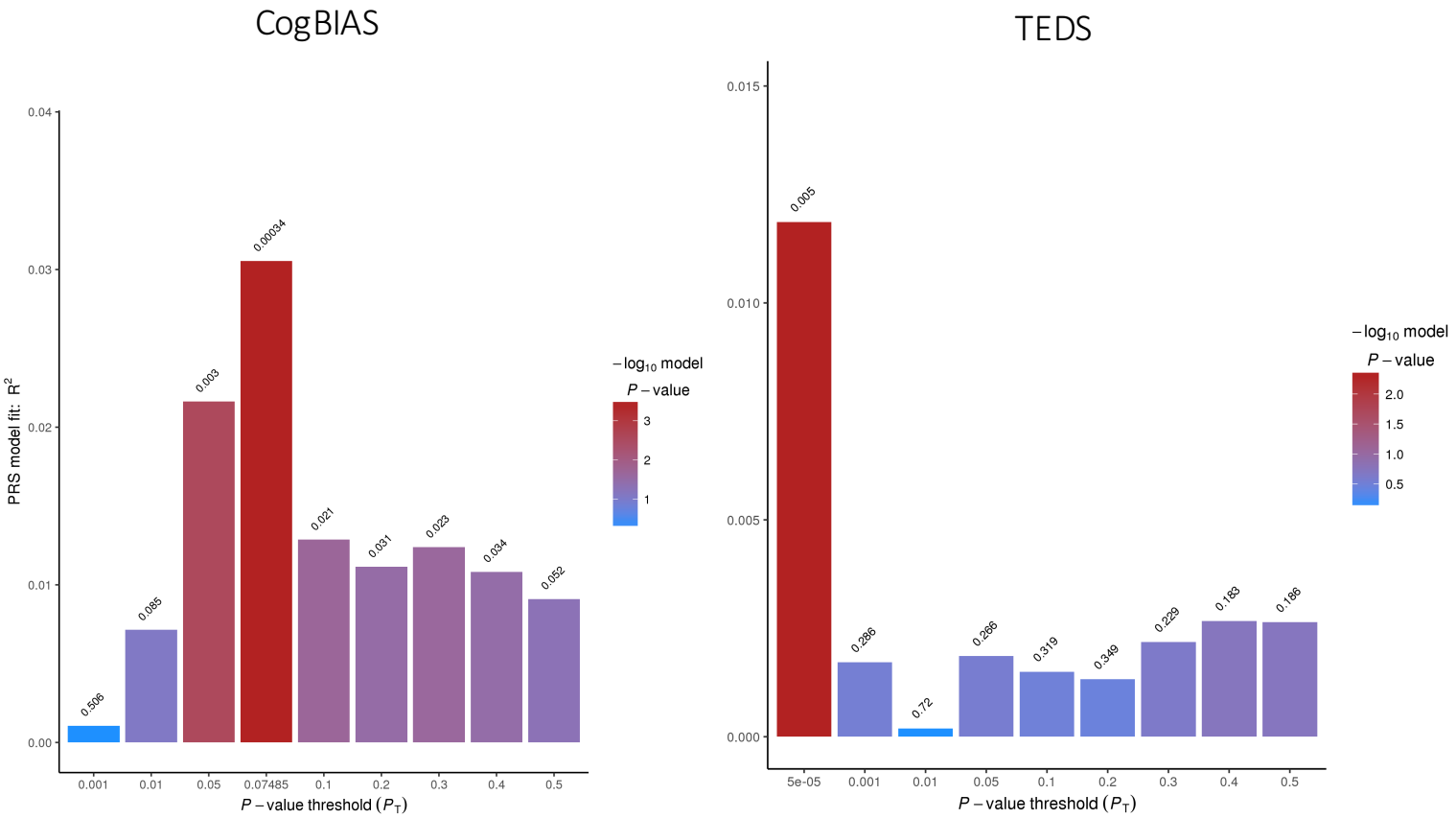

Figure 4.7 INSOMNIA

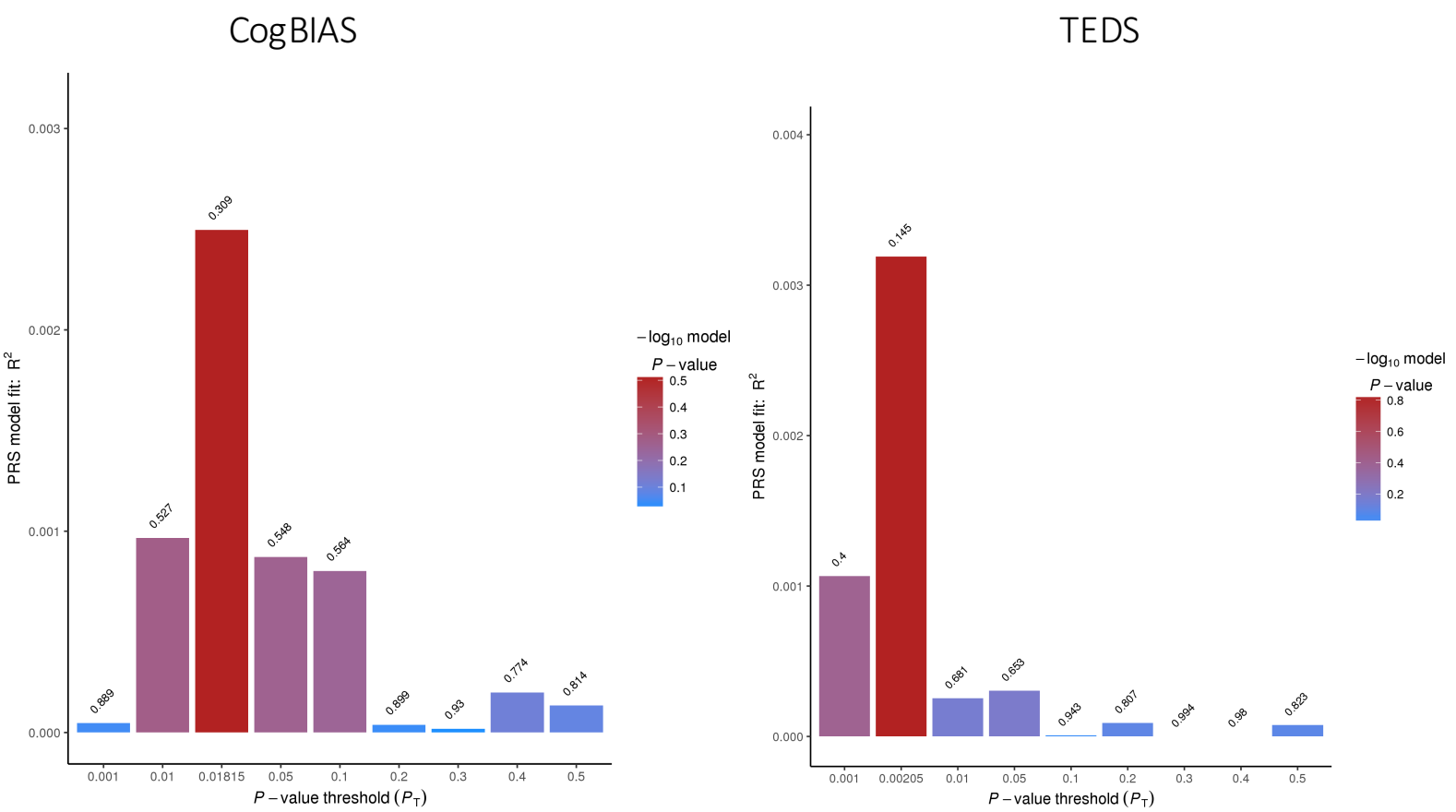

Figure 4.8 LONLINESS

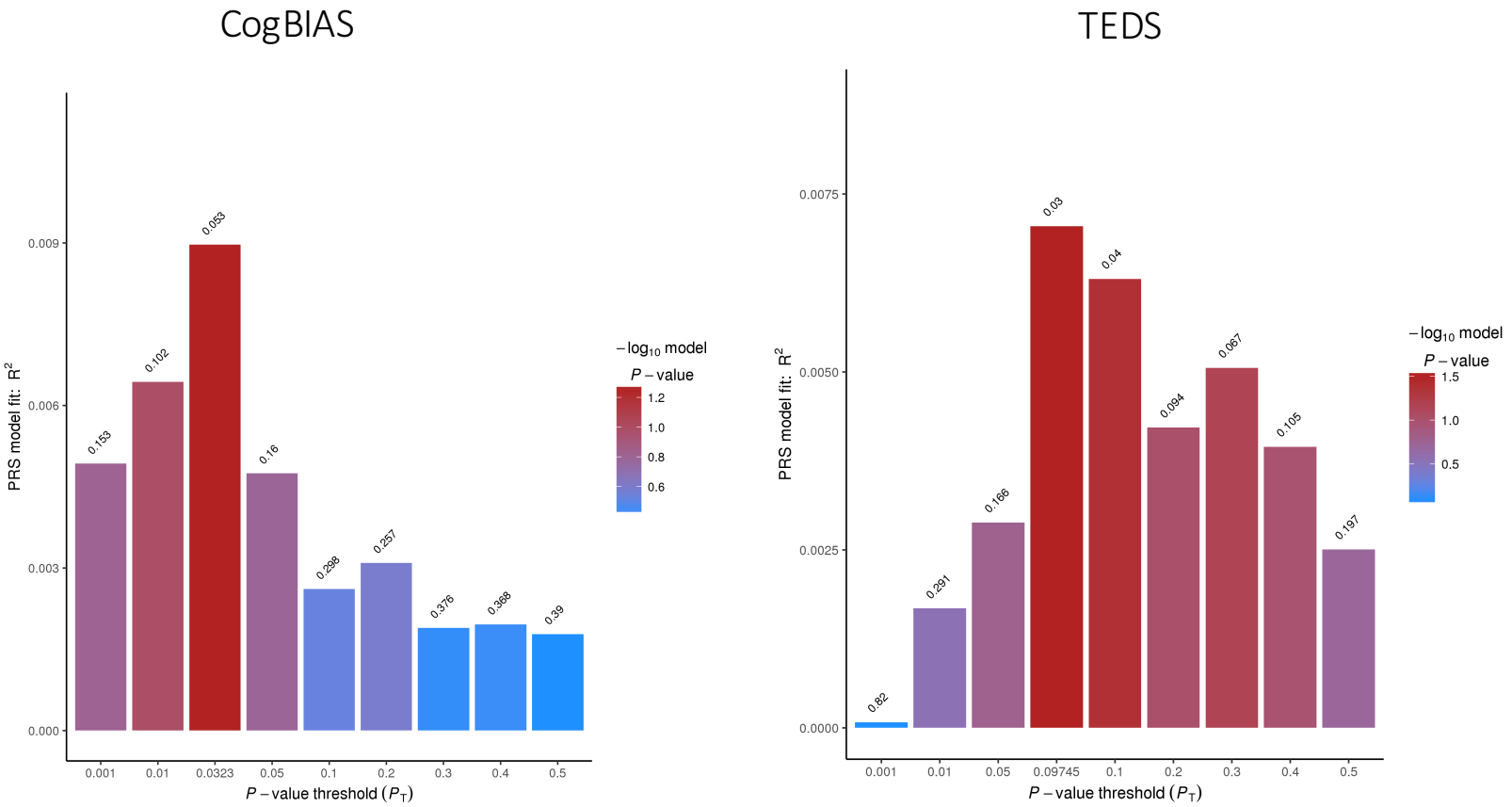

Figure 4.9 NEUROTICISM

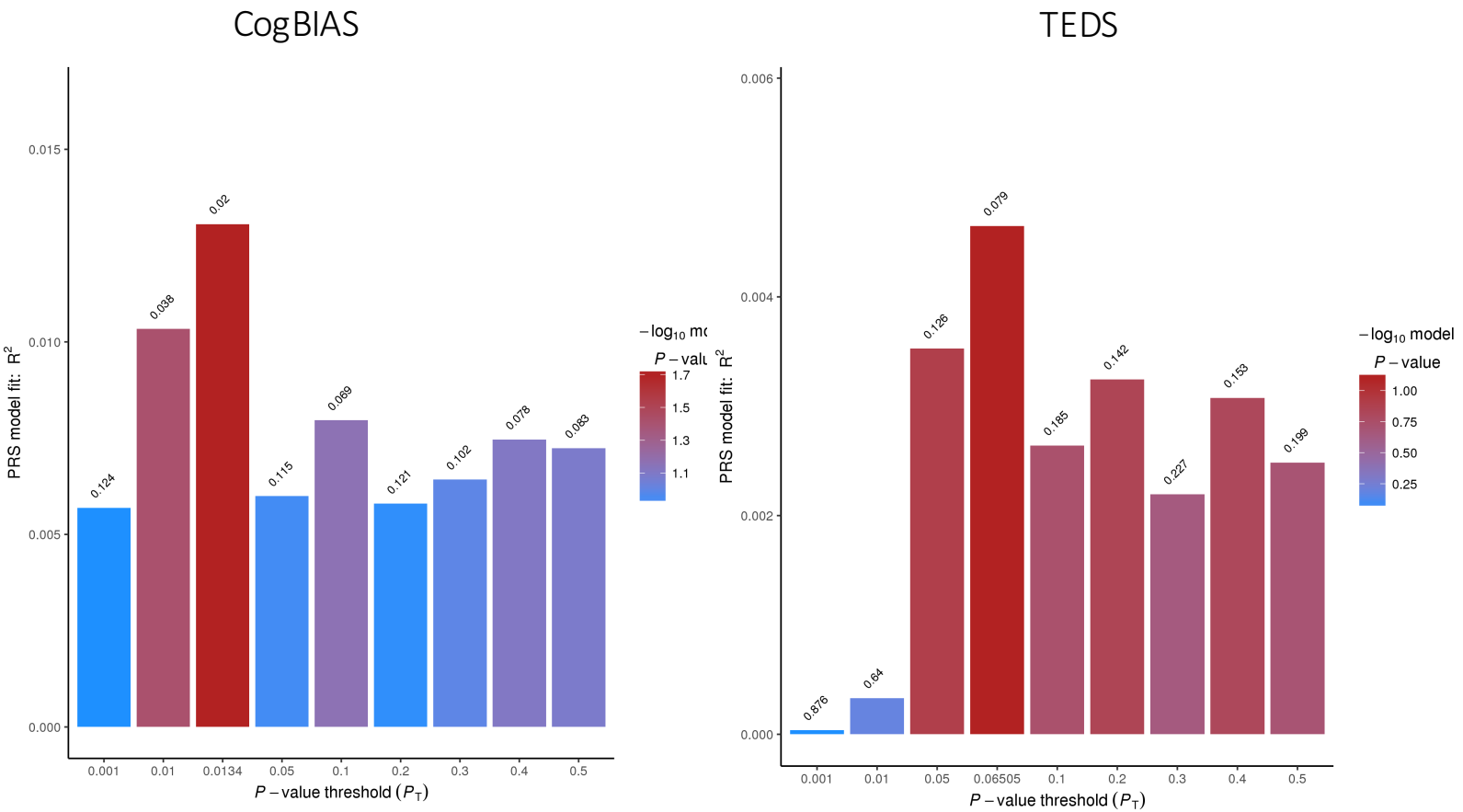

Figure 4.10 OPNENESS

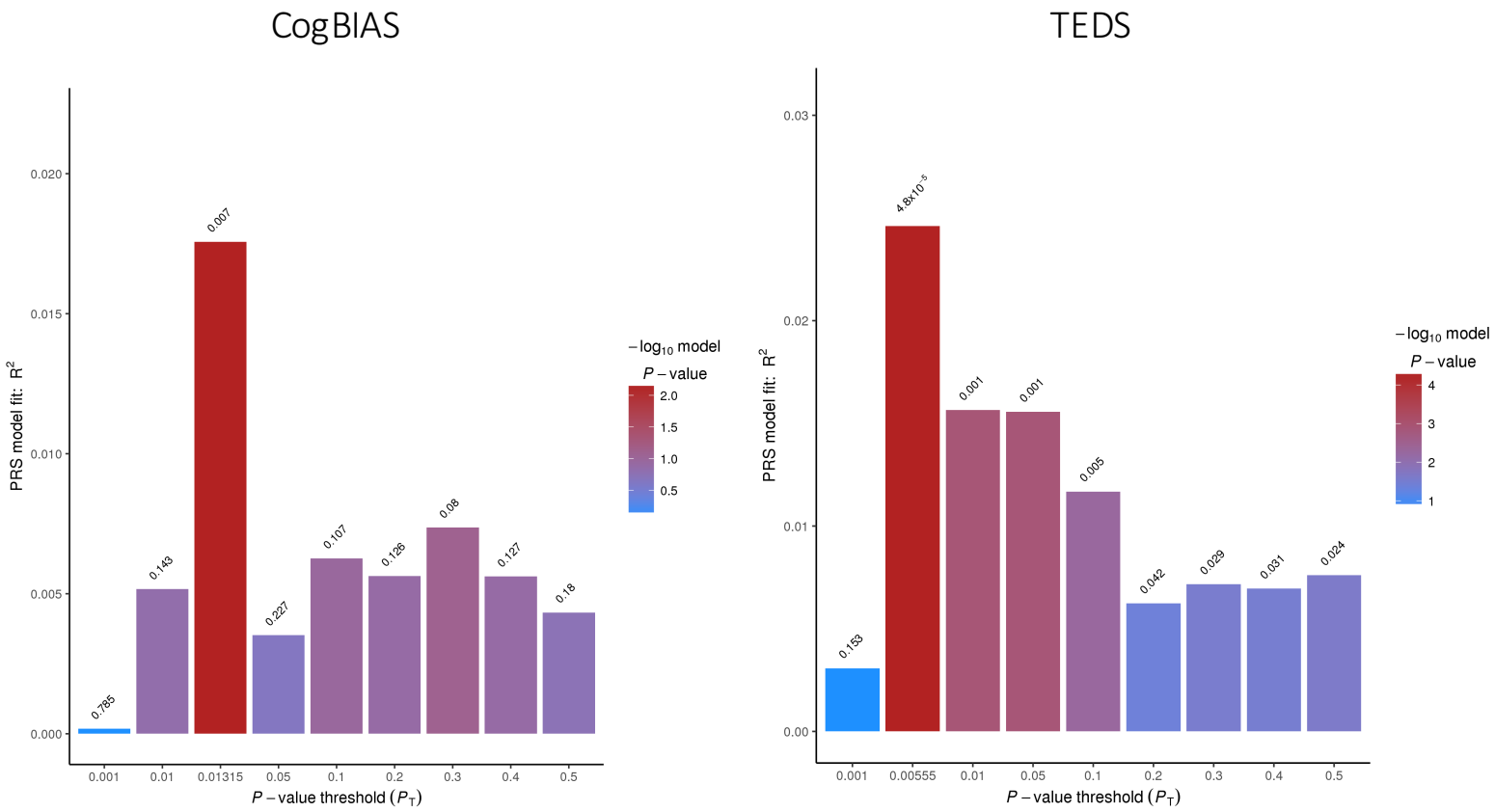

Figure 4.11 SUBJECTIVE WELLBEING

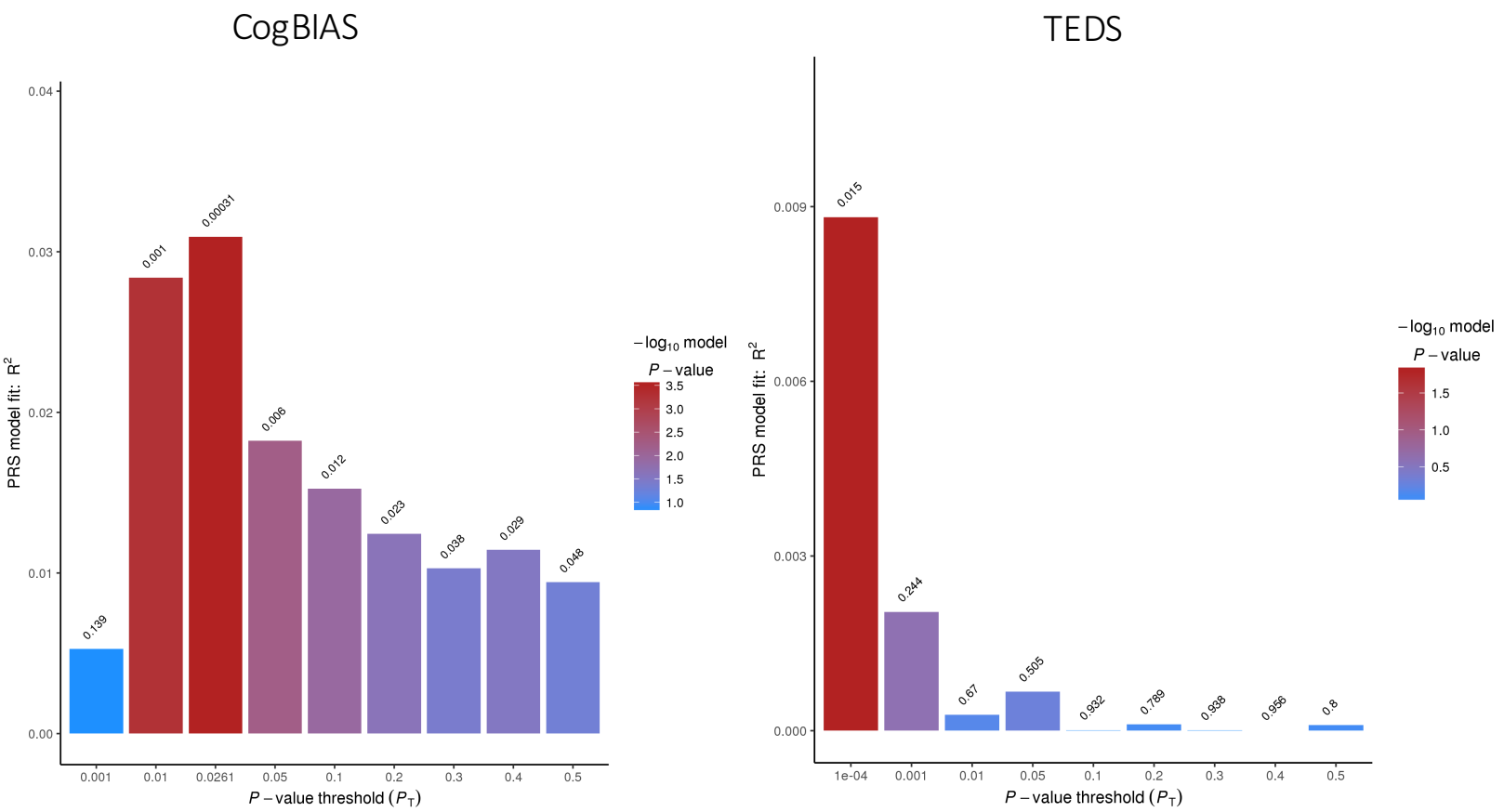

Figure 4.12 ADHD

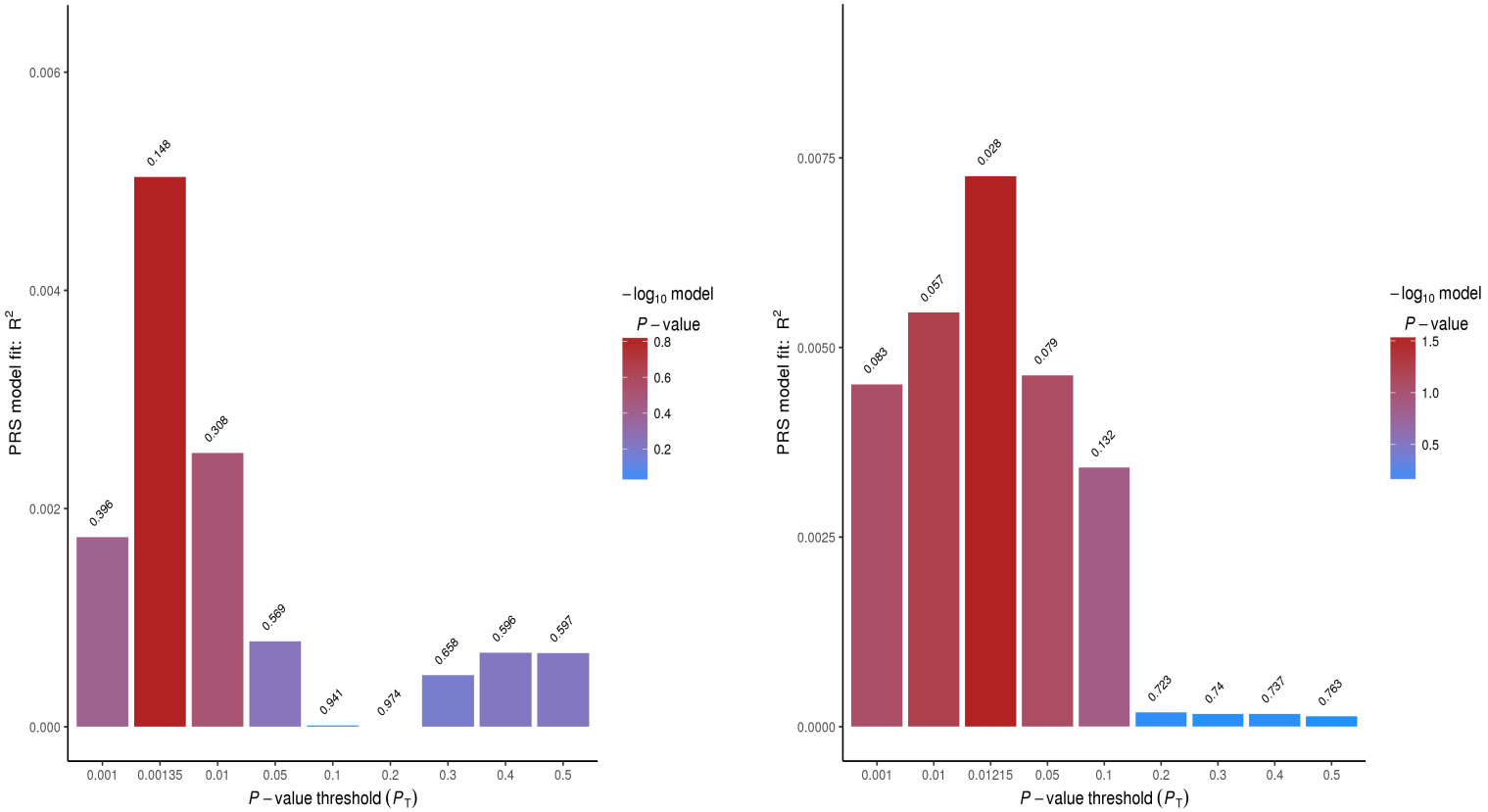

Figure 4.13 AUTISM