Introduction

“Children of the world” by Sam van Druten, 9 years old
Stress, Vulnerability and Resilience, a Developmental Approach

1.1. Scope
This thesis is devoted to the field of individual differences in behaviour and emotions, and started out with the study of multiple effects of genetic, neurophysiological and environmental influences during life on the outcome in young children. In this thesis we are interested in the interactive influence of genes and environmental factors in child populations across different cultures. Understanding their influence will stimulate better outcomes in children.

1.2. Aims and outlines
The aim of this thesis is to investigate influences of genes and environments on behavioural, emotional and cognitive outcomes in different samples, most derived from the general population. A developmental approach will be used to understand how nature (genotypes) and nurture (e.g. environmental risk or protective factors) interact to determine developmental outcomes. A biopsychosocial model is used to describe the interactions between genotypes, stress in-utero and stress later in life, as well as protective factors.

1.3. Biopsychosocial model
The biopsychosocial model used in this thesis covers a timeline from preconception until adolescence. This model describes the influences of the history of parents and the environment in-utero in interaction with genotypes on the outcome of a child at birth. After birth many other environmental factors in interaction with genotypes, most of all parenting and life events, have a further influence on socio-emotional and cognitive development of the child. These environmental influences are heterogeneous, meaning they can be protective or a potential risk. For example ‘good’ parenting is a protective factor, while ‘bad’ parenting (for example parents who neglect their children) is a risk factor for development of psychopathology in the child. Essential is how children appraise and cope with these events in life. The child’s appraisal influences the impact of the stressor on the child (Lazarus and Folkman, 1984). To illustrate this, if a child considers a new school as an opportunity to meet new children the events will be less stressful than when a child is anxious to meet new children.

Our model describes the interactions between environment and genotypes of the parents, the fetus and child. Genotypes moderate environmental effects (Rutter, 2002), through effect on susceptibility to risk environments. In other words, an adverse environment has little effect if the genetic susceptibility is absent, while it may have a large effect when the genetic susceptibility is present. For example, Caspi et al. (2002, 2003) found that allelic variation in the monoamine oxidase A (MAOA) gene interacts with maltreatment on antisocial behaviour in young people and the allelic variation in the serotonin transporter gene interacts with traumatic experiences on the occurrence of depressive disorder. However, social circumstances also influence the effects of environmental stress. For example, social support is a key regulator of stress. As a consequence, the interactions between environment and genotypes must be placed against the background of social factors such as socioeconomic status, culture, community, religion, peer group, extended family etc. See model 1. The social factors mentioned here are broadly defined and most of all influence other risk factors. For example the effect of low socioeconomic status is not an effect directly of the economic pressures themselves, but is mediated by family functioning and...
parent-child relationships (Conger et al., 1994; Costello et al., 2003a). This underscores the importance of parenting on the development of the child. The final outcome of cognition and socio-emotional development of the child will determine its vulnerability or – in absence of psychopathology although exposed to adversities – its resilience.

Model 1.

\[ \text{Gt} = \text{genotype, Gff} = \text{genotype father, Gtm} = \text{genotype mother, Gti} = \text{genotype infant, E} = \text{environment, } \times \text{ = interaction effect, for example: GtxE = interaction between genotype and environment} \]

Although our biopsychosocial model describes a timeline until adolescence, risks and protective effects are important during the whole life cycles and not only confined to early life.

2. Background

2.1. Why a developmental approach?
During the last 50 years there have been dramatic changes in our understanding of mental disorders (Rutter, 2010; Rutter and Smith, 1995). One such change is the awareness of the prevalence and impact of psychiatric disorders in childhood (Costello et al., 2003b). Research findings reveal that most of the psychiatric disorders arise before adulthood (Costello et al., 2006). In recent years, studies have focused on the complex interaction between biologic and environmental factors and their influence on brain function, behaviour, emotion and cognition, and in the end: mental disorders. This approach is called 'developmental
psychopathology. Developmental studies seek to explain the principals underlying changes in behaviour and cognition during development. From a developmental point of view, mental health is not a state, but an outcome of dynamic processes over years, in which the individual is shaped by genotype in interaction with different environmental experiences during life (Rutter et al., 1997). An important aim in developmental studies is to understand the relation between genes and environmental influences, also in the past referred to as ‘nature versus nurture’. In the past the difference between nature and nurture was thought to be stricter, with philosophers like Descartes (1596-1650), Rousseau (1712-1778), Darwin (1809-1882) and Gesell (1880-1961) being nativists, who believed that behaviour is strongly influenced by genes, while environmentalists emphasized the importance of experience in life. For example, John Locke (1632-1704) thought the mind was a ‘tabula rasa’, a blank slate written on by experience. Locke, as well as Freud (1856-1939), are known for their emphasis on early life experience. Freud saw the infant as vulnerable, with parenting as the most important influence on development. However, like many more modern psychologists and psychiatrists, Freud already believed in an interactive model between nature and nurture, and he rejected the perspectives of nativists (nature) and environmentalists (nurture). He thought that nature produces the unconscious functioning of the mind, and that this functioning interacts with experiences in early life (mainly parents) (Eng, 1980).

Recently it has become clear that nature and nurture indeed should not be considered separate influences, but rather two parts of a constant interaction that contribute to the unique development of an individual (Rice et al., 2010; Rutter et al., 1997). The influence of both genotypes as well as environment starts from conception, although some may argue that it even starts prior to conception. For example, the way in which nutrition and health status of the mother and father influence the quality of the eggs and sperm (Vujkovic et al., 2009; Westphal et al., 2004). The interaction between genotypes and the environment is a clearly dynamic process. This is called gene x environment interaction (G x E interaction). G x E interaction is present when the effect of genotype on the development of psychopathology depends on the level of exposure to an environmental factor (Rutter et al., 1997). Environmental factors have a direct influence on the activity of genes, meaning that the same individual will develop differently under different circumstances (Belsky and Pluess, 2009; Meaney, 2010; Rutter et al., 1997). For example, children carrying the S allele of the SERT gene will only exhibit suicidal behaviour later in life if they experienced traumatic experiences in early life. This implies that traumatic experiences, as an environmental factor, interact with the genotype of the child (Caspi et al., 2003).

Thus, the challenge does not concern the independent influence of genes or environment on a certain outcome, but rather the understanding how they interact with each other. For studying these effects you can use different study designs. One way to study genetic and environmental effects and interactions between them is by using cohort studies. Cohort studies offer the advantage of collecting time-dependent exposure information before the onset of psychopathology (i.e., a prospective approach). This approach provides opportunities to identify individuals with a higher risk at an early stage, which is critical for developing interventions and understanding pathways leading to psychopathology. However, causal relationships cannot be clearly identified as confounders may complicate the associations between exposure and psychopathology. For example, is an individual depressed because of bullying in the past (causal relation), or is an individual, who is prone to bullying, also more
prone for developing depression (for example because of internalizing traits)? This problem is not an issue for G x E interactions as it is for pure environmental effects. Another useful design is a case-control study, especially in comparing environments (Hardt and Rutter, 2004; Thomas and Greenland, 1985). Although both cohort and case-control studies are at risk for measurement errors, in case-control studies environments can differ systematically between cases and controls. For example, children with depressive symptoms might recall their history as more negative than children without these symptoms. However, this problem does not exist in measurement of genotype, and that makes the case-control design a good choice for studying associations between genotypes and risks for psychopathology (Clayton and McKeigue, 2001). Furthermore, for G x E studies it is important to identify the effect of functional genetic polymorphisms that might affect this risk factor (Clayton and McKeigue, 2001).

2.2. Stress

Environmental influences most typically include demanding, stressful events ('stressors') from the in-utero period through to adulthood. The result of stressors is called stress. The term stress is difficult to define and quantify (Hobfoll, 1988; Lazarus, 1993), but most researchers use some variant of Selye's definition that “stress is the non-specific response of the body to any demand made upon it”. In this sense stress can be considered as a metabolic concept. Selye considered favorable events (e.g. taking a new job) as well as unpleasant events as stressors. He proposed that stress can be viewed in a positive or neutral way and referred to this as 'eustress'. He stated that 'eustress' is the amount of stress needed for an individual to live an active, healthy life, while he used 'distress' when levels of stress exceed an individual's ability to adapt to stress (Selye, 1975). Distress is considered to have a negative effect on health (Bicanic et al., 2008; Langeland and Olff, 2008; Selye, 1982).

Selye developed a model of stress, which he called the General Adaptation Syndrome (GAS). The GAS has three stages; first the ‘alarm’ stage, where the brain detects a threat or stressor triggering physiological arousal. The second stage is ‘resistance’ where the body adapts to the stressors and homeostasis is achieved. The last stage is ‘exhaustion’, which occurs after prolonged resistance, a reaction to the constant high metabolic demands of an extended alarm stage. During exhaustion the body's energy stores and hormone reserves are being depleted, which may upset homeostasis and leave the individual vulnerable to disease. This condition could lead to stress-related conditions such as atherosclerosis, hypertension or depression, as the stress response systems become exhausted (Selye, 1982).

A number of physiological processes change in response to environmental stress, including the production of stress-related hormones. There are two different important physiological stress systems; the sympathetic adrenergic medullary axis (SAM) and the hypothalamic pituitary adrenal axis (HPA). The SAM axis is a quick response system, with immediate sympathetic activation and release of catecholamines such as adrenaline and noradrenaline from the medulla of the adrenal glands (de Vente et al., 2003). Norepinephrine is also released within multiple brain circuits. Adrenaline and noradrenaline are both known as ‘arousal hormones’ and activate the cardiovascular and neuroendocrine functions. The SAM axis mobilizes and diverts energy to muscles, heart, and brain while at the same time it reduces blood flow to the internal organs and the gastro-intestinal system. During the stress response only the essential organs function and energy is conserved through the suspension
of the non-essential systems, such as the digestive system (Henry, 1992; Porges, 1991; Ursin and Off, 1993).

The HPA axis is a slower response system which has the function of ensuring vital organ functioning in response to ongoing stress for energy expenditure. The HPA axis starts with release of corticotrophin-releasing hormone (CRH) from the hypothalamus to the pituitary gland. After stimulation by CRH (often acting with vasopressin) the pituitary gland releases adrenocorticotropic hormone (ACTH), which circulates through the bloodstream to the adrenal cortex. ACTH causes the adrenal cortex to synthesize (among other steroid hormones) corticosteroids. Corticosteroids cause the suspension of the digestive system and the immune system, and promote the liver to release sugar and lipids for rapid energy utilization (Harbuz and Lightman, 1992). The main glucocorticoid hormone in humans is cortisol (Engelmann et al., 2004; Gómez et al., 1998). Cortisol is often deregulated in stress related disorders, e.g. PTSD (Off et al., 2006). However, cortisol is not necessarily an indicator of distress, but rather associates with metabolic challenges (Harbuz and Lightman, 1992; Miller and O'Callaghan, 2002). For example, there is a circadian variation of cortisol release with a rise in cortisol in the first 30 minutes after awakening that is linked to preparation for metabolic demands of the upcoming day after a fasting period of time. Cortisol also rises after other increases of metabolic demand such as sexual intercourse, physical exercise, and food intake (Hoffman-Goetz and Pedersen, 1994). As cortisol is not simply found to be a 'stress' hormone, its relation to psychopathology is not yet clear (Meewisse et al., 2007).

The fast pathways of arousal are also called the 'fight or flight response', as these reactions take place to allow the body to physically deal with the stressors it is confronted with. It was described by Cannon as an evolved response by mammals to threat (Hoffman-Goetz and Pedersen, 1994). However, stress reactions can be maladaptive. For example, today stress responses may arise to psychological problems for which there is no reason for a 'flight' response as was required in the evolutionary past when threats to survival were more prevalent and severe (Christopher, 2004; Peleg and Shalev, 2006; Raison and Miller, 2003). Although Selye's GAS presupposed the same response to a variety of stimuli, later studies showed that specific perceptions of control result in different patterns of neuroendocrine activation (Henry, 1992; Peacock and Wong, 1990). Lazarus and Folkman (1984) proposed a cognitive theory of stress, referring to the meaning of an event to the individual. They developed a model, which focuses on the transaction between people and the external environment (known as the Transaction Model). The stressor may in fact reside in the individual's perception of the event's implications for him, making stress the consequence of appraisal and not the antecedent of stress. According to this theory, the way an individual appraises an event plays a fundamental role in determining the magnitude of the stress response (Lazarus and Folkman, 1984; Off et al 2005a). This has also physiological implications. For example, exposure to stressors that are viewed as challenging, tend to result in significant elevations of serum catecholamines with no change in serum prolactin or cortisol. It enhances immune function (McEwen, 2000). In contrast, exposure to chronic stressors that are viewed as overwhelming, tend to result in marked elevations of serum prolactin and cortisol with no change in serum catecholamines. Sustained activation of the HPA axis with chronic elevated cortisol levels has been associated with degeneration of the hippocampus, deficits in hippocampus-dependent memory tasks, affective distress, perceived uncontrollability, prolonged major depressive illness and with a range of somatic problems such as
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sugar imbalances, decreased bone density, higher blood pressure and lowered immunity (Lupien et al., 1997; Lupien et al., 1998; McEwen 1998, 2006, 2008, Olff, 1999; Olff et al., 2005b). To identify the health consequences of intense, repeated, and sustained activation of bodily systems is currently a major objective for stress research.

One of the psychiatric disorders that can develop after a stressful event is Posttraumatic Stress Disorder (PTSD). The defining characteristic of a traumatic event is “the capacity to provoke fear, helplessness or horror in response to a threat of injury or death” (Yehuda, 2002). A diagnosis of PTSD requires that a person is exposed to an extreme stressor or traumatic event to which he responded with fear, helplessness or horror (Yehuda, 2002). PTSD is not uncommon after many types of traumatic events. Nearly all people experience the acute form of the disorder (Acute Stress Disorder) at some time in their lives (Breslau et al., 1998; de Vries and Olff, 2009). While severe, such reactions usually subside within hours to days, if the stressor does not continue. Interestingly, studies show that the psychological and biological response to a traumatic event is not mainly determined by the characteristics of the event, but by the characteristics of the person involved (Olff et al., 2005b; Yehuda, 2002). The neurophysiologic responses between people are different, as well as their subjective interpretations of the event, which are both influenced by previous experiences (Olff et al., 2005a). This will have an important influence on the stress response. Thus, after a traumatic event, the unique characteristics of the person determine if an individual develops PTSD (Peleg and Shalev, 2006; Yehuda, 2002).

PTSD is diagnosed in adults as well as adolescents and children. Of note, in children responses to stress are age-dependent and strongly influenced by the reactions of adults (mainly their caregivers). One of the coping mechanisms of young children (infants and preschool children) is searching for protection by crying and clinging towards their caregiver. Because they generally lack the developmental skills to effectively cope with stressful situations by themselves, children are particularly dependent on family members for comfort (Lerner and East, 1984; Skinner and Zimmer-Gembeck, 2007). Even for anticipation to danger, the young child will rely on his caregiver by looking at his facial expression, also called ‘social referencing’ (Boer, 2009). For this reason, on some occasions children in this age-group may be as affected by the reactions of their caregivers as they are by the direct effects of the stressor.

Both the ‘fight or flight’ reaction in older children and adults, as well as increasing search for comfort by caregivers in younger children in reaction to stress have the function of protection and will increase survival (Boer, 2009; Gunnar and Quevedo, 2007).

2.3. Vulnerability by genetic influences

For years it was believed that statistical associations between environmental risks, such as life events and development of psychopathology, only represented environmentally mediated risks effects. The field of behavioural genetics created a major change in this thinking. A growing body of evidence suggested the importance of G x E interactions and suggested that a considerable degree of the effects of risk environments were actually genetically driven (Plomin, 1994; Plomin and Bergeman, 1991; Rowe, 1994; Rutter and Silberg, 2002; Scarr, 1992).

Results from neurobiological and epidemiological studies have increased our understanding of developmental influences on behaviour, emotion and cognition. Because of the known
high heritability of behavioural traits and intelligence, more genetic studies as well as G x E studies have been undertaken over the past few years. Genome-wide association studies, an approach that relies on the data produced by the International Human HapMap Project (Hardy and Singleton, 2008; Plomin et al., 2009), find associations between genotypic variation and risk factors of psychiatric disorders, which reveal ‘candidate genes’, associated with particular endophenotypes related to psychiatric disorders. For example, the end phenotype ‘high reaction time variability’ on continuous performance tests in children with attention deficit hyperactivity disorder (ADHD) is associated with dopamine receptor DRD4 7-repeat allele absence (Kebir et al., 2009). Another example is the association found between the serotonin transporter promoter region (5-HTTLPR) and suicidal behaviour and depression related personality traits (Levinson, 2006).

At a molecular level, DNA interacts with signals from the environment, which together influence the expression of a trait in the context of a particular environment (Bagot and Meaney, 2010). Thus, having a certain genetic variant in itself does not mean that a particular trait will develop. For example, rhesus monkeys with secure early attachment relationships are resilient for the otherwise increased risk for adverse developmental outcome of the ‘short allele’ of 5-HTT by ‘maternal buffering’ (Suomi, 2006). The majority of genes are expressed as the proteins they encode. This process occurs in two steps: first transcription, which creates a complementary RNA copy of a sequence of DNA, followed by translation, the creation of a protein from messenger RNA. DNA methylation involves the addition of a methyl group to DNA. Methylation is crucial for normal development and has the function of cellular differentiation. DNA methylation alters gene expression by regulation of gene transcription. Methyl groups generate a local chromatin configuration that renders the genes inaccessible, and thus transcriptional inactive (Altwood et al., 2002; Cedar, 1998; Jaenisch and Bird, 2003).

It is suggested that for many disorders, different genetic loci impinge on a common pathway to pathogenesis. Thus, finding risk alleles and protective alleles for a particular disorder will provide clues to other risk loci by which variability at the same pathway can contribute to disease in interaction with the environment.

2.4. Resilience

Individuals differ in their response to stress. Individuals who do not develop disorders and illness despite exposure to risk factors are referred to as resilient. Garmezy, Masten and Tellegen were the first to discuss the concept ‘resilience’ in 1984 (Garmezy et al., 1984). They described resilience as “manifestations of competence in children despite exposure to stressful events”. In 1985 Sir Michael Rutter defined resilience again as “facing stress at a time and in a way that allows self-confidence and social competence to increase through mastery and appropriate responsibility” (Rutter, 1985). In 1994 Masten defined resilience as “successful adaptation despite risk and adversity” and “a pattern over time, characterized by good adaptation despite risk and adversity” (Masten, 1994). Gordon in 1995 defined resilience in the following way: “resilience is the ability to thrive, mature and increase competence in the face of adverse circumstances, including biological, psychological and environmental circumstances” (Gordon, 1995).

However, it is not easy to clearly define the concept ‘resilience’. In later studies resilience is often measured as absence of (mental) health problems despite experience of traumatic
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events/disasters (Bonanno et al., 2006, 2008). However, most of the times resilience is defined intuitively and not empirically. Resilience differs from both social competence and positive mental health as resilience is defined contextual (Rutter, 2006a). Environmental factors that lead to resilience in one context may not lead to resilience in other circumstances. Hence, ‘academic resilience’ may be related to other individual characteristics and environmental factors than ‘emotional resilience’. Furthermore, because resilience in relation to childhood adversities may be influenced by positive adult experiences, a life span trajectory approach is needed (Rutter, 2006a).

Researchers have documented that protective resources can interact with existing adversities to influence behaviour, emotion and health outcomes (Davey et al, 2003; Fossion and Linkowski, 2007; Heaven and Carrochi, 2007; Rew and Horner, 2003). The approach of protecting youth from harm through promotion of protective factors has sparked great interest in resiliency-based research (Rutter, 1993). Resilience is partly influenced by predisposing genetic and biological factors, but is also acquired and developed by for example emotional and secure attachments with parents or significant others, and by social learning (Buckner et al., 2003; Rutter, 2006b).

2.5. Cultural differences

As causes, expression and prevalence of disorders are different between ethnic groups (Bur- chard et al., 2003), cultural background cannot be neglected in research. Rather than ignoring cultural differences, scientists should be conscious of the importance of increasing replication studies in other countries. In this thesis one study was performed in a Dutch cohort and 4 studies were performed in a Singaporean cohort. The Netherlands is a European country with 16.7 million residents. It has a multicultural population, although the majority of the residents is Dutch. The Netherlands is a democratic state, has a capitalist market-based economy and is seen as a liberal country given the drugs legalisation policies and legalisation of euthanasia. The Gross Domestic Product (GDP) in the Netherlands in 2009 was 792.128 billion US dollars (source: World Bank). The Gini coefficient, as a measure of income inequality (value of 0 expressing total equality and a value of 100 maximal inequality) was 30.9 in 2007 (source: CIA World Factbook). The homicide rate in the Netherlands in 2009 was 0.92 per 100,000 inhabitants (source: Dutch homicide statistics). In 2010 the birth rate was 10.3 births per 1000 residents (source: CIA World Factbook). The life expectancy has been quite stable over the last 50 years (slightly increasing) to 80.4 years in 2008 (source: World Bank). Around 3000 psychiatrists are registered, of which quite a large number work part-time. The suicide rate was 0.85 per 100,000 inhabitants in 2009 (source: World Health Organization).
Singapore is a South East Asian island country off the southern tip of Malaysia, with a highly developed market-based economy. It has a multicultural population of 5+ million people, mostly made up by Chinese, followed by Malay and Indians. Singapore is a parliamentary republic and establishes a representative democracy, although one party has dominated the political process since 1959. Singapore laws include judicial corporal punishment in the form of caning, and death penalty for first degree murder and drug-trafficking. Criminality rates are low. In 2009 the homicide rate was 0.38 per 100,000 inhabitants (source: United Nations Office on drugs and crime division for policy analysis and public affairs). The GDP was 182.23 US billion dollars in 2009 (source: World Bank). The Gini coefficient was 48.1 in 2008, representing more income inequality than in the Netherlands (source: CIA World Factbook). The birth rate was 8.65 births per 1000 residents in 2010 (source: CIA World Factbook). The life expectancy has increased over the last 50 years up to 80.7 years in 2008 (source: World Bank). In Singapore 152 psychiatrists are registered, of which most of them work full-time. The suicide rate was 10.3 per 100,000 inhabitants in 2006 (source: World Health Organization). Of note, in Singapore suicidal attempts and suicide are offenses by law.

There is increasing awareness to incorporate culture and diversity into the study of stress and resilience (Arrington and Wilson, 2000; Ungar, 2006, 2008). Parenting, social learning, coping styles and some other core psychological factors associated with resilience are influenced by culture. Hence, resilience is expected to differ among different cultures. One important difference between cultures is the way stressors are perceived. For example, although school work and academic performance are major stressors for children worldwide, the level of educational stress varies among different societies (Steinberg et al. 1992). Among them, the highest pressure to succeed and do well academically is found in Asian cultures. For example Steinberg et al. (1992) found that Asian American students spend twice as much time each week on homework than students of other ethnic groups living in the United States. The Asian American students also reported that their parents had high expectations and would be disappointed if they came home with any grade lower than A (Steinberg et al., 1992). Also in Korea it was found that children spend twice the time on studies and less time on socializing and leisure activities than their American counterparts (Lee and Larson, 2002).

It has been suggested that the focus on studies is related to the belief in Asian countries that graduating from a (high ranking) university is a passport to a good job and a high social status (Chung et al. 1993; Steinberg et al., 1992). As a consequence, Asian families strongly emphasize to their children the need to succeed educationally (Mordkowitz and Ginsburg, 1987). Shame and loss of face are frequently used in Asian cultures as socialization tools to reinforce familial and cultural obligations, societal expectations and proper behaviour (Yeh and Huang, 1996). Not meeting one’s own expectations and/or the expectations of significant others is a serious matter that can potentially result in loss of face and loss of confidence as well as support from one’s family and even the community (Yeh and Huang, 1996). In Singapore, Isralowitz and Hong found in 220 high school students that ‘being pressured to keep up with the schoolwork’ was ranked as the top problem or concern of students (Isralowitz and Hong, 1990). In another national youth survey in Singapore, the majority of young people ranked education as the most stressful aspect of their lives (Ho and Yip, 2003).

Two studies showed that Dutch children have a high quality of life and feel less pressured by education in comparison to children in other industrialized countries in Europe.
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The most recent publication is from a British study of the University of York, published in 2009, carried out among children in 29 European countries (27 EU countries plus Norway and Iceland). They included 43 life circumstances that influence happiness, such as infant mortality, obesity and poverty. In each category The Netherlands scored best (Child Poverty Group, 2009). A study done of Unicef (Unicef, 2007) examined happiness of children on the basis of 6 criteria: material wealth, health, education, relationships, safety, and children's own feelings of luck. The Dutch children had the best scores in comparison to 17 other European countries plus Canada and the United States. They found that, aside from material quality, Dutch children expressed the greatest amount of 'subjective well being' in response to questions about whether they like school, feel pressured by school and how they rate their own health. Dutch children are generally happy with the compulsory educational system with relatively low pressure and they enjoy the best relationships with their parents (judged by the ease children can talk to their parents about various topics) and friends (Unicef, 2007).

Another important difference between cultures is family bonding. While in most European countries there is a focus on individualisation and self-development, in Asia the focus is on strong family bonding and interdependency. The stigma of mental disorders is high in Asia and many problems are addressed within the family. Although the prevalence of mental disorders in Singapore is roughly the same as found in Europe or Australia (Fones et al., 1998), the outcomes can be different. For example the outcomes for schizophrenic patients are better in Singapore, probably associated with the high family care (Kua et al., 2003). Furthermore, in Singapore 'domestic helpers' are commonly employed by families. This helper typically lives in close proximity with the family providing continuous assistance in household matters, child care or care for elderly. It is important to understand that children raised under these circumstances are likely to have different experiences, with parenting influences not only from their biological parents, but also from living-in grandparents and domestic helpers.

2.6. Limitations of previous development studies in gene and environmental influences on childhood outcomes

Individuals, from childhood onwards, respond differently to stress (Broekman et al., 2007; Langeland and Olff, 2008; Olff et al., 2005b). Most developmental studies have focused on children with problem behaviour or psychiatric problems to understand the effect of stress and adversities on socio-emotional and cognitive outcomes. Although it might be more difficult to study the effects of risks and protective studies in a general population, this is of utmost importance, because most children will belong to this group. Hence results of these studies will be more applicable to daily life and can improve the health of a larger group of children. However, these studies are rare.

For example, most PTSD studies have focused on extreme situations such as war and terrorist attacks or natural disasters. However, posttraumatic stress can develop also in more common situations such as traffic accidents or medical surgeries (Kotinimie et al., 1996; Langeland and Olff, 2008; Siegel, 1988). Detection of susceptibility to develop posttraumatic stress symptoms is important for prevention, but is hampered by inherent unpredictability of stressful events. That is why most studies are done in retrospect.
Another example is studies examining the effect of birth weight. To date most of these studies focus on children born with a low birth (i.e. <2500 grams) or very low birth weight (i.e. <1500 grams), or children born premature. Although these studies were important to show the impact of fetal growth on neurodevelopment and socio-emotional outcomes (Bhutta et al., 2002; Black et al., 2008; Victora et al., 2008), they do not apply for most children within the normal birth weight range. Studies conducted in normal birth weight children are rare and often show contradictory results, for example for the influence of birth weight on cognitive function (Christensen et al., 2006; Gale et al., 2004; Lawlor et al., 2006; Matte et al., 2001; Pearce et al., 2005; Shenkin et al., 2004; Tong et al., 2006).

Studies on developmental origins of socio-emotional behaviour reveal pronounced effects of G x E interactions but focused mostly on specific psychiatric problems in adolescents and adults, such as affective disorders (Caspi et al., 2003; Kendler et al., 2005; Risch et al., 2009). However, it is equally important to understand the role of genes in a general population, but G x E studies examining differences in socio-emotional characteristics in ‘healthy’ children are rare.

Also studies examining resilience are seldom performed in a general population. Most studies focus on high-risk samples of children, such as children who suffer from diseases, children from broken families and children who live under extreme adversities. Although these studies are important, they do not provide a broad perspective of resilience for children in the general population. Moreover, established risk factors have been studied extensively for over many years, but only over the last years studies have started to focus on protective factors as well (Richardson, 2002). Furthermore, it is expected that concepts of resilience are cultural sensitive. So far, there has been no universal resilience scale, which enables a more objective outcome of resilience measured in different cultures. Although population studies on resilience have been done in school aged children living in the United States and Europe (Backett-Milburn et al., 2003; Rew et al., 2010; Shapiro and Lebuffe, 2006; Tschann et al., 1996), no resilience studies have been performed to date in Asian school aged children.

3. Outline of the thesis

3.1. Studies in genetic vulnerabilities

The intriguing question is: why do some people develop mental health problems after a stressful or traumatic event, while others do not? Chapter 2 provides a review of the literature about genes which, in interaction with a traumatic event, may be involved in the development of PTSD. Variation in these genes might explain variation in outcomes across individuals. This article will give a firm overview to understand genetic effects on unique individual outcomes.

In chapter 4 we examine G x E influences on the outcome of children in socio-emotional development in the general population, measured with the Child Behavior Checklist (CBCL). We study the interaction between birth weight corrected for gestational age (as a reflection of early life influences) and genotypes involved in the serotonergic system. Our hypothesis is that different genotypes will moderate the effect of stress in-utero on the socio-emotional outcome in school aged children.
3.2. Studies in early life stress in-utero
In chapter 3 a cohort study is described which examines early life adversity in-utero (reflected in birth weight, birth length and head circumference) on IQ in children, measured with the Raven’s Progressive Matrices. The hypothesis is that a lower birth weight, a shorter birth length and a smaller head circumference at birth, within the normal birth proportion range, will reflect a less optimal environment in-utero and will predict a lower IQ than children who had a high birth weight.

The study in chapter 4 describes the influences of the environment in-utero in interaction with genes involved in the serotonergic system on the outcome in socio-emotional development (see studies in genetic vulnerabilities).

3.3. Study in stress during early childhood
Medical procedures, if planned in advance, may provide an opportunity to investigate the stress response in a prospective way because they are stressful in nature, especially for young children. In chapter 5 we examine the influence of a medical procedure on the outcome of behaviour and emotion (measured with the CBCL) and posttraumatic stress symptoms (measured with the Impact of Event Scale) in Dutch children. Our hypothesis is that stress of a medical procedure will have a negative influence on the behavioural and emotional state of children. We also hypothesize that the neurophysiologic states (measured by Respiratory Sinus Arrhythmia and cortisol) as well as the temperament styles of children (measured with the EAS temperament survey) will predict the outcome of posttraumatic stress, behaviour and emotion of the child after a medical procedure.

3.4. Studies in resilience
In chapter 6 we describe a cohort study which attempts to approach real life complexity between common risk factors and adversities as well as common assets and protective factors during development on cognition (IQ, measured with Raven’s Progressive Matrices) and academic results (report of school) as well as behavioural and emotional outcomes in children (measured with the CBCL) in Singapore. Our hypothesis is, that in comparison to studies done in the USA and Europe, for Singapore different protective factors and risk factors are important in influencing mental wellbeing and academic performance.

In chapter 7 the development of a resilience scale for a Singaporean population is described.

3.5. General discussion
The main conclusions, implications, limitations and strengths of our studies are described in chapter 8, as well as proposals for further research and investigations.

3.6. Summary
An English and Dutch summary of all studies is provided in chapter 9.