Stress, vulnerability and resilience: a developmental approach
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General discussion

“Helicopter view” by Maai Wentink, 5 years old
1. General discussion

This thesis consists of studies that attempt to offer a developmental framework to promote greater understanding of common influences and experiences during early life in interaction with genotypes on outcomes later in childhood. In particular how nature (genotypes) and nurture (e.g. environmental risk or protective factors) interact to determine socio-emotional and cognitive outcomes.

The emphasis is on studies done mainly in a general population to examine the impact of (early) life influences in the majority of children instead of children with rare diseases or children living in extreme or aversive situations. We assessed (early) life influences from a neurobiological, social and a psychological perspective using the biopsychosocial model below. Model 2 shows the variables and results of our studies.

Our studies acknowledge the hypothesis that all experiences during life, including early experiences in-utero, will influence the expression of genes with associated effects on socio-emotional and cognitive outcomes later in life, which determine the vulnerability or resilience of an individual.

In this chapter our findings from clinical, epidemiological and epigenetic studies are discussed, with incorporation of a review of the latest insights gained from relevant research in this field.

Model 2.

Chapter 8

1.1. Stress and genetic influences in-utero

Many previous studies have shown that early development in-utero influences later development. For example, in-utero environments, maternal stress and diet, birth weight, and growth by one year of age seem to program offspring growth and metabolic pathways, altering life long susceptibility to diseases later in life (Bale et al., 2010; Barker 1998, 2007; Fogel, 2003; Gluckman et al., 2005; Gluckman and Hanson, 2005, 2006a, 2006b; Rutter 2006b; Rutter et al., 2006). Although the effect of early in-utero development on physical illnesses was already known, more recent studies relating to psychiatry, psychology and neuroscience have found that early in-utero development also influences the development of vulnerability for mental disorders later in life (Gale and Martyn, 2004; van den Hove et al., 2010; Wiles et al., 2005). For example, a recent study showed an association between smaller ganglionic diameters in brains of infants of 6 weeks old and higher internalizing scores on the Child Behavior Checklist (CBCL) at age 18 and 36 months (Herba et al., 2010). Many other studies have described the association between early life stress in-utero and depression later in life (Gale and Martyn, 2004; van den Hove et al., 2006). Hence, an optimal environment in-utero (in interaction with the genotype of the fetus) is important for optimal development, not only physically, but also psychologically (Gluckman et al., 2005).

The stress diathesis model (Francis et al., 1999) proposes that the association between early experiences and health risks later in life, is determined by neurodevelopmental pathways that produce individual differences in neural and endocrine responses to stress (Boer, 2009; Francis et al., 1999; Meaney et al., 2007; Wiles et al., 2005). The hypothesis is that stress in-utero causes excess release of corticotrophin releasing hormone (CRH) as well as cortisol. Increased exposure to these hormones has a negative influence on birth weight and associates with impaired feedback regulation of the HPA axis and serotonin signaling in the key brain areas (Kajantie and Raikkonen, 2010; Weinstock, 2010). This hypothesis has found support in animal studies (Weinstock, 2010). Thus, prenatal stress in rodents results in decreased hippocampal glucocorticoid receptor expression, impaired feedback inhibition and increased HPA responses to acute stress. In line with this, Goland et al. (1993) showed that increased umbilical cord levels of corticosteroids are indeed associated with growth restriction. In conclusion, these findings suggest that unborn babies are capable of making ‘life history adjustments’ in anticipation to the expected threatening environment by investing less in growth to increase their survival (Bateson et al., 2004; Gluckman et al. 2007; Gluckman and Hanson, 2004).

Our studies in in-utero development showed an effect of fetal growth on Intelligence Quotient (IQ), as well as on socio-emotional traits associated with affective disorders. In chapter 3 we describe our results, which showed a clear linear relation between birth weight, birth length and head circumference and IQ. For children within the normal birth weight range it was found that for every additional kg in birth weight, every additional cm in birth length and every additional cm in head circumference, IQ showed an increase with 0.50 up to 2.70 IQ points in the multiple adjusted model. This suggests that intrauterine growth retardation is associated with a lower IQ. These findings are in accordance with those of other studies in Western countries (Eide et al., 2007; Hollo et al., 2002; Rahu et al., 2010), although our study is the first study to report a positive association with IQ, later in childhood (after 4 years). Interestingly, IQ has been positively related to health later in life (Batty et al., 2007). This suggests that one explanation of the association between fetal growth and health might
be indirectly, through effects on IQ. Optimal circumstances during early development also seem to be associated with better outcomes in terms of socio-emotional development. Children with a birth weight (corrected for gestational age) just above the mean had lower internalizing scores, modulated by genes involved in the serotonergic system (TPH2, HTR2A). Interestingly, genotypic variation of TPH2 and HTR2A genes has been associated with an increased risk for affective illness later in life in adults before. Our results suggest that genotypes of TPH2 and HTR2A determine the influence of fetal growth. These findings are consistent with emerging ideas that variation in gene expression might regulate sensitivity to environmental conditions, and that developmental outcomes are context-specific. The hypothesis about change in activity of genes by experiences during life, without alteration of DNA, is seen as 'epigenetic programming' (Meaney and Szyf, 2005).

Another study with robust results showing context-specific effects of genes involved in the serotonergic system is that of Caspi et al. (2003) in New Zealand, who demonstrated in a sample of 847 people that those with a short allele of the serotonin transporter gene were more likely to become depressed when they experienced adverse life events than those with only long alleles. Caspi and his colleagues suggest that the relation between stressful events and depression is modulated by genotypes (long-long, long-short, short-short alleles) of the serotonin transporter gene. A large meta-analysis of 12,500 people (including the New Zealand study of Caspi et al.) could not replicate this finding (Risch et al., 2009). However, not all included studies were of good quality. Furthermore, laboratory studies, which were not included in this meta-analysis, have shown that humans with the short allele indeed show greater biological stress responses (Gotlib et al., 2008). In line with this, it has been found that people with the short allele are more vulnerable to disorders such as post-traumatic stress disorder and anxiety (Gotlib et al., 2008).

Epigenetic effects were also demonstrated in an impressive study by McGowan et al. (2009). They examined epigenetic differences in the glucocorticoid receptor promoter in the hippocampus postmortem in suicide victims with a history of childhood abuse in comparison with suicide victims without such a history. The results showed an association between physical and/or sexual abuse and lower expression of the GR gene due to methylation, which inhibits gene expression by blocking transcription factor binding. Decreased function of GR is associated with higher sensitivity for stress and depression (McGowan et al., 2009). This is in line with earlier studies done in rats, which clearly demonstrated the influence of maternal care on hypothalamic pituitary adrenal axis (HPA) function by epigenetic programming of the glucocorticoid receptor expression (Fish et al., 2004). In conclusion, environmental influences lead to alteration in gene expression, either increasing or decreasing the impact of sequence variation.

1.2. Stress during life, resilience and cultural influences
In chapter 5 we describe a study, which examines the influence of a medical procedure on young children. Most children had lesser behavioural and emotional problems after surgery without symptoms of posttraumatic stress, suggesting that these young children are generally quite resilient towards this stressor. There were no significant differences between children with different temperaments, although emotional children did have worse outcomes in general.
Although we initially proposed that children who are highly sensitive to stress do have more behaviour and health problems, Boyce and Ellis (2005) propose that high stress sensitivity is not always negative. They found that children with high stress sensitivity are not only more sensitive to negative experiences, but also to positive experiences. Those children are more likely to develop mental problems when growing up in adversity, while on the contrast, more reactive children were better able to thrive when living in protective circumstances. This suggests that this group of children is more sensitive to the supportive and nurturing qualities of those protective environments (Obradovic et al., 2010). This effect could explain our finding in chapter 5 that high stress reactivity measured by RSA and cortisol was not a predictor in itself of the response to a surgical procedure. It is likely that other positive influences, such as high quality parental and hospital care, could have had a positive influence on the outcomes. We suggest that more vulnerable children are characterized as those with increased emotional reactivity and environmental adversity, such that emotional reactivity alone is not a sufficient condition for the prediction of vulnerability.

The recent proliferation of research in resilience is not surprising given the well-documented associations between resilience and mental wellbeing. Every individual encounters unavoidable, painful events and hardships in the process of growth and development. The development of an individual is an active process of adaptation within his environment (Nakaya et al., 2006). Resilience is the absence of illness and dysfunction despite exposure to risk. The overarching aim of resilience research has been to increase understanding of underlying mechanisms of resilience to promote resilience-enhancing behaviours, and in turn mental health. Many studies demonstrate the negative effects of serious life adversity by focusing on low-income children, orphans or abused children. For example studies showed that children living in poverty or children with traumatic experiences were more likely to have problems with academic achievements or social adjustment (Pungello et al., 2010). However, in the study contained in chapter 6 we examined both risk factors as well as protective factors in children from the general population. This study showed that risk and protective factors do have a differing impact on the outcome in IQ and school results along with socio-emotional functioning. Although protective factors (high intelligence, higher education father and occupation father) have an impact on both academic capacities as well as socio-emotional development, risk factors (negative spousal conflict resolution, negative methods of discipline, chronic health problems, negative life events and developmental delay) only influence socio-emotional development in Singaporean children, without having a major effect on academic capacities. These findings parallel those of the effects of poverty in children (Hackman et al., 2010). Thus the quality of the home environment, especially the degree to which it affords cognitive stimulation, predicts academic outcomes. Poverty associates with reduced cognitive stimulation and poorer academic performance. Poverty also associates with marital conflict and parenting problems, such as those described above. Parenting mediates the effects of poverty on socio-emotional, but not academic outcomes (Hackman et al., 2010). Interestingly, in this study we found some differences in risk factors with earlier findings from the other studies done in European countries. For example, family structure and surrogate caregiving were relatively less important risk factors than in Europe and the USA. This might be related to differences in culture, as Singaporean children are more often raised with surrogate caregiving by living-in grandparents and/or domestic helpers, while in the USA and Europe parents more often use daycare for children.
Previous studies have found that the social context can influence behaviour directly, as it influences individual beliefs and norms (Pasick et al., 2009). This finding underscores that resilience is a contextual concept and measuring resilience should be culturally sensitive. Although resilience is a worldwide concept and mechanisms and determinants of resilience are universal, local cultural influences cannot be neglected. In chapter 7 we developed a resilience scale (SYRESS) for Singaporean adolescents, in addition to the existing resilience scales developed in the USA and Europe. The fact that patterns and expressions of resilience are context-dependent is discussed. Although the domains of the SYRESS evidently reflect universal mechanisms and determinants of resilience, our findings show that the SYRESS is a more comprehensive resilience scale than existing resilience scales for Singaporean adolescents.

2. Conclusions

In conclusion, research in stress and resilience should always take contextual factors into account. Genetic forces do not operate independently of environmental forces (Meaney, 2010). That means that studies need a dialectical perspective of interconnection between biology and environment, including cultural differences (Sameroff, 2010). This supports a need to understand epigenetic mechanisms as a critical determinant for mental health predisposition. Nature and nurture interact to shape the unique human individuals. A developmental approach is useful to explore those influences.

3. Implications

Understanding the interactions between genotypes and environment during development on cognitive and socio-emotional outcome later in childhood is important for clinical practice as well as public health. When a child or adolescent is suffering from a mental disorder, parents tend to blame the child: why is our child not listening? Why is he so naughty? Alternatively, many professionals may first react by blaming parents: why is this child not listening, what is wrong with their parenting? However, it is not an issue of blame, as it is about the interaction between the characteristics of the child as well as the direct environment during their life: “It is both the characteristics of the child and the parents, the neurons and the neighborhoods, the synapses and the schools, the proteins and peers and the genes and government”, as Sameroff explains in his article (2010). Adopting a life span perspective will help to emphasize the multiple factors during life which influence the development of the child and help to diagnose problems. The interconnection between genotypes and environment has to be implemented in clinical sciences of psychiatry and psychology. Hence, targets for intervention should focus on child, parents, and the environment.

Experiencing adversity early in life does not always cause developmental problems. The process of interaction between genes and environment is not static. Children have the potential to change and recover. Protective factors are therefore critical to identify and to exploit in the development of new and more effective therapies. Cognitive, temperamental,
health or emotional shortfalls can be compensated for by strengths in other dimensions, and
skills associated with positive adaptation can be cultivated and practiced (Richardson, 2002;
Richardson and Waite, 2002; Waite and Richardson, 2004). For example, research in neuro-
science has shown the enormous plasticity of the prefrontal cortex, which is important for
emotion and self-regulation, into the early twenties (Dahl, 2004). Furthermore, although IQ
seems to be rather stable from 10 years onwards, there is evidence that interventions during
adolescence can affect neurocognitive skills (Cunha et al. 2006). Other studies showed that
effects of poverty on emotional and cognitive development can be mediated by parental
factors (Conger et al., 1994), and that IQ is subject to the effects of early intervention
programs (Ramey et al., 1979).

Although we did not focus on parenting in our studies, it is clear that the role of parenting
should not be underestimated. In humans and animal models, both the quality and quantity
of early-life maternal care showed to be a predominant signal triggering changes in activity
of genes including genotypes involved in the HPA axis, associated with the development
of resilient or vulnerable phenotypes. Fish et al. (2004) showed the importance of maternal
licking and grooming in mother rats for somatic growth and stress sensitivity in their
offspring. In humans, it is known that maternal stress predicts the cortisol levels of the child
(Lupien et al., 2000). This finding suggests that parenting skills can influence the activity of
genotypes that regulate stress responses and neural development directly, making the child
more or less vulnerable to stress. At the same time it is implying that high quality parenting
can improve the stress reactions in children by regulating the activity of genes. Indeed, studies
have shown that for example hippocampal volume is influenced by parental care, and that
hippocampal development remains plastic until late childhood/adolescence, with considerable
evidence for reversibility (Belsky and de Haan, 2011; Bredy et al., 2004; Buss et al., 2007).

In conclusion, genotypes influencing neural and endocrine stress responses are ‘plastic’.
Therefore the impact of prenatal adversity on neural development can be modulated
by the quality of postnatal care. This obviously has implications when targeting clinical
treatment programs. Parent-child interventions emerge as a target for prevention in high
risk populations. Studies have shown that these interventions can be effective (Ramey et al.,
1979). Interestingly, these parent-child intervention studies also showed G x E effects. For
example Bakermans-Kranenburg et al. (2008) showed that video-feedback interventions, to
promote positive parenting and sensitive discipline, were effective in decreasing daily cortisol
in children with the dopamine receptor D4 (DRD4) 7-repeat allele, but not in children
without DRD4 7-repeat allele (Bakermans-Kranenburg et al., 2008). They also discussed
the role of oxytocin and serotonin genes on sensitive parenting and social interactions with
offspring (Bakermans-Kranenburg and van Ijzendoorn, 2008). Another study suggests that
oxytocin might be even useful in treatment of stress symptoms as it reduces the fear response
(decreasing amygdala activation, inhibiting fear response, and enhancing extinction learning)
and increases social interaction (activating social reward-related brain regions increasing
engagement in the therapeutic alliance) (Olff et al., 2010).

Other helpful clinical interventions can focus on ‘building resilience’, teaching children stress
management skills by adopting problem-focused, cognitive-focused and emotion-focused
coping techniques to manage problems.

The idea of a life span approach to psychiatric disorders is also of huge potential importance
for public health policy. The concerns of society have always been put in a life-span perspec-

Chapter 8

124
Healthy productive adults are needed to continue a successful culture and economy. Whilst scientists will study cognitive and emotional development for an intellectual interest, governments are interested in the same studies to prevent behavioural problems that are costly for society. Life-time studies are thus often well supported by governments; evidence based interventions are needed to improve life outcomes for human resources. Research in developmental psychology aims to examine origins of individual differences in emotions and behaviour, which is the basis for extensive intervention or prevention programs for mental health problems (Fisher et al., 2000). However, these programs for prevention of mental health problems and resilience building will need to be valued in different cultures and environments. For example, a study showed that behavioural inhibition of toddlers was positively associated with mothers’ punishment orientation towards the child and negatively associated with mothers’ acceptance and encouragement of achievement towards the child in a Canadian sample, while these directions of associations were opposite in a Chinese sample. Interestingly, in the Chinese sample behavioural inhibition was associated positively with mothers’ warm and accepting attitudes towards their children and negatively with rejection and punishment of their children (Chen et al., 1998). Another example of the important influence of the environment on traits is provided by Kerr et al. (1997). They showed that the best trait for survival among males living in high criminal societies was behavioural inhibition, while behavioural inhibition is associated with affective disorders in more safe societies. This finding suggests that temperaments of individuals show different adaptations in different environments and across cultures in particular (Chen et al., 1998). Before developing an intervention program for resilience building (like improving coping skills), it is important to explore the factors associated with resilience in children from different countries and raised under different environments.

One way to prevent psychopathology is by reducing important social risk factors for a given environment, such as poverty and low quality education. Remediation can be offered to disadvantaged children by governmental actions. A study by O’Connor et al. (2000) showed in a study of adopted Romanian infants reared in severely deprived orphanage environments, that the later an orphan was adopted, the lower was his cognitive performance as an adult. Also secondary school classroom remediation programs designed for children with cognitive deficits showed poor outcomes, while empirical literature shows high economic returns for remedial investment in young disadvantaged children (Cunha et al., 2006). This implies that remediation and help for reducing social risk factors should be done as early as possible. Furthermore socio-emotional skills should be promoted. It is known that socio-emotional skills also foster cognitive skills and promote healthy behaviours. Especially emotionally nurturing environments will produce more capable learners, which is important for human resource (Cunha and Heckman, 2007; Schweinhart et al., 2005). This suggests that family or parenting interventions in disadvantaged families can improve socio-emotional and cognitive function in children.

National interventional programs can be used for resilience building. For example the “Understanding the Adolescent Project” in Hong Kong (Lee et al., 2007; Lee, 2006; Shek et al., 2006; Shek, 2006) seeks to influence problem-solving skills, effective communication with peers and adults, techniques to create win-win situations, and the early identification of the elements of a stressful situation with encouraging results. In the Netherlands several resilience building programs are well accepted. One example is the Marietje Kessels Project
for children of the normal population of 10 to 13 years old, which is given in 12 sessions during school times with the purpose to increase resilience by increasing awareness of abuse and unacceptable behaviour. Research showed that it has a positive effect on resilience building of children (van Helvoort and Claris, 2005; van der Vegt et al., 2001). However, policy should not only focus on improving childhood circumstances, but also on interventions to improve early growth by improving obstetric and neonatal care. This should be available for all mothers, regardless of their socioeconomic status. As mothers of lower socioeconomic status are at risk for less optimal nutrition and lower birth weights (Freising et al., 2006; Ricciardi and Guastadisegni, 2003; Watson and McDonald, 2010), it is extremely important that this group is included as well. Good infant and maternal health can have a significant positive impact on the future health and wellbeing of offspring. Birth weight of a child is widely accepted as a key indicator of infant health. Birth weight can be affected by a large variety of factors, including age, size, health, stress level and nutritional status of the mother and the use of toxins, which all have a direct influence on the quality of the in-utero environment. Some of these factors can be influenced. Olds et al. (2002) describe perinatal interventions that reduce fetal exposure to alcohol or nicotine with long-term effects on cognition, socio-emotional skills and health in offspring (Olds et al., 2002). Other preventive options to think of are offering nutrient supply, education for mothers-to-be and regular checks during pregnancy on the growth of the baby by scans etc. The evidence for interventions in low-birth-weight children so far suggests that early interventions can be effective (Bonnier, 2008).

4. Strengths

A major strength of the studies in this thesis is that most studies are done in the general population. Previously many studies focused on difficult or disadvantaged circumstances or children with a psychiatric disorder to examine factors relating to genotypes, stress and resilience. It is therefore not easy to generalize these results derived from ‘populations at risk’. For example it is clear that low birth weight carries an increased risk for developing mental disorders (Schmidt et al., 2010). However, in this group of children there are multiple pathophysiology that can arise that do not inform the extent to which the fetal environment within the normal birth weight range can affect children. Our studies in early development show that there is also a clear influence of birth parameters within the normal birth weight range on cognition and, in interaction with genotypes of the serotonin system, on socio-emotional development. We used large sample sizes and well validated instruments and made use of multiple birth parameters. In our G x E study we used relatively large genetic subgroups, which might have helped us to find independent effects of each genotype. This made it possible to study interaction effects as well, which will be more difficult to demonstrate in smaller subgroups. We selected only polymorphisms with evidence of functionality in previous studies. It is likely that the power was sufficient to detect a large effect size and it is unlikely that the number of significant findings can be explained by statistical chance. On top of that, our results of the involved genotypes which showed a vulnerability to develop internalizing traits, are in accordance with earlier studies which showed associations between those genotypes and af-
To understand differences in the stress response of children, it is important to be able to study this within the same environmental conditions. For traumatic and stressful experiences, this is obviously a challenge. In our semi-experimental study for children with an indication for an adenotonsillectomy we used a standardized surgery. Subsequently we were able to do pre-assessments of physiological, temperamental and psychological factors as well as post-assessments to study differences in the stress response in a prospective way. We also included physiological measures, which allow the direct measurement of the emotional state instead of being dependent on indirect measuring through parent report.

While previous studies most of the times focused on older children, adolescents and adults, we examined children of different age groups including preschool children. The impact of stress will differ according to the developmental stage (Boer et al., 2009). In preschool children more often externalizing symptoms are reported aside from internalizing problems in reaction to a traumatic experience, while in middle childhood and adolescence mainly internalizing problems are reported (Boer et al., 2009). However, studies done in children of preschool children are rare and rely most of the times on parental report only (Boer et al., 2009). In our ENT study we were able to use more objective measures in addition to the subjective parental report. In this study of young children (M = 3.7 years, SD: 1.5) we found no indications for the development of externalizing or internalizing problems. However, in our resilience study in chapter 6 we examined older children (M = 9.4 years, SD: 1.7) with indeed more children scoring in the clinical range of the internalizing problems (15.1%) than externalizing problems (7.2%).

A strength of our resilience study (chapter 6) is the inclusion of protective factors. Positive factors are often neglected in studies. Combining both risk and protective factors allows improved understanding of ‘real life’ influences on socio-emotional and cognitive outcomes in children. Another strength of this study is the objective measurement of academic results by performance scores received from the schools.

Finally, an important strength in this thesis is that studies were performed in different cultures and by doing so, we became more aware of the influences of culture on the measurement of stress experience and resilience. For example, IQ was measured with the Raven Progressive Matrices, as this is the IQ test which best excludes differences in language and culture. Second, in the epigenetic study, an ethnically homogenous sample was selected. Only Chinese children who had a mother as well as a father from full Chinese heritage were included to exclude any influences of ethnicity on the outcome. Furthermore, in the study of development of a resilience scale, important similarities as well as differences for the concept resilience worldwide were discussed, which has implications for measuring and comparing issues of resilience worldwide.

5. Limitations

In general in all our studies selection biases, loss to follow-up, and demographic differences between included and excluded children could have influenced outcomes. An example of indications for a possible sample bias can be found in the study of early life influences on IQ in chapter 3. The average IQ was relatively high and even the relatively lower birth weight...
and shorter birth length siblings had higher IQ's than expected in a general population. An example of differences between included and excluded children was shown in the resilience study in chapter 6, in which the non-responders showed a lower socioeconomic status. This makes us wonder if this sample is representative. Although most studies used a reasonable to large sample, in the ENT study (chapter 5) the number of examined children was limited. Artifacts in neurophysiologic measurements and missing data in this study further reduced the numbers. This could have influenced the power to detect differences between different temperaments and the outcome after surgery.

Studies used self-report questionnaires of behaviour, which render subjective information. For younger children parental self-report was used, in elder children aside from self-report, reports from teachers and school results were included to increase objectivity. In the studies using the CBCL, differences in scores of the CBCL seem not to be that large. However, the CBCL is a subordinate scale, with more differences in scores in the higher range. Our results show an expected percentage in the clinical range, conform previous studies.

Some of the instruments used were not yet validated for the particular cultural population, for example the CBCL norms are validated in the Netherlands, but still need to be evaluated in Singapore. Previous studies done in Asia found different cut-off scores for the CBCL and TRF. Another limitation is that the Raven's Progressive Matrices does not cover such a complete IQ score as can be obtained from other current full batteries, but focuses more on IQ domains of abstract reasoning. On the other hand, the RPM is a well chosen instrument as it is a nonverbal IQ test which minimizes cultural influences, which is needed in a multicultural population such as Singapore. Another limitation is that IQ was measured in early to middle childhood. However, IQ in early to middle childhood is not a strong predictor for later IQ. IQ scores become stable by age 10, suggesting a sensitive period for development of IQ below the age of 10 (Schuerger and Witt, 1989). Previous studies have shown that the association between birth weight and IQ becomes weaker later in childhood, probably due to other factors which play an increasingly important role in the development in cognition of children (Boomsma et al., 2001; Tong et al. 2006).

We did not explore differences in gender, with exception of the prospective ENT surgery study. Previous studies, however, have shown that gender is an important factor in stress responses. For example, a recent animal study found that prenatal stress was associated with a clear increase in anxiety-and depression related behaviour in male Sprague-Dawley rats, but not in female rats (van den Hove et al., 2010). In humans it was found that females showed increased depressive symptoms when born at low birth weight, while boys did not (van Lieshout and Boylan, 2010). Also, low birth weight seems to be associated with higher autonomic nervous system response in females, and with higher peripheral vascular resistance and HPA responses in males (Kajantie and Raikonen, 2010). In our ENT surgery study we found indications for a difference in response between boys and girls. Although the number of girls was small, girls showed more internalizing scores after surgery in comparison to the Dutch norm group, while boys showed more improvement in behavioural and emotional health after surgery. It is well established that gender has an influence on the prevalence of many mental health disorders in adults, with women generally being more prone to internalizing problems such as anxiety and depression and men being more prone
to externalizing problems and substance abuse (Pratchett et al., 2010; Seedat et al., 2009; Smith et al., 2008). Even small gender differences have been found in childhood affective disorders (Franić et al., 2010). Gender specific acute psychobiological reactions to stress and gender differences in perception of control and social support have all been described as important factors in stress reactions (Olff et al., 2007; Zahn-Waxler et al., 2008).

Most of our studies are limited by the chance of residual confounding as it was not feasible to include all environmental factors. Even in the resilience study, in which we included a reasonable number of protective and risk factors. For example, in this study we did not include temperament of the child, although a difficult temperament can have worse outcomes in presence of family conflict, while family conflict has no effect on children with an easy temperament (Rutter, 1999). Another important factor which was missing in our studies was parenting. For example the effect of children's birth weight on the development of psychiatric disorders has shown to be moderated by maternal warmth in low birth weight children (Tully et al., 2004). In line with this, it is known that the association between low birth weight and major depressive disorder is higher in children of depressed parents, which suggests that parental depression may augment the impact of birth weight on offspring (Nomura et al., 2007). Also the duration of breastfeeding has been described as a protective factor against behavioural problems (Golding et al., 1997). A magnetic resonance imaging (MRI) study has shown that parenting modulated the association between birth weight and hippocampal volume in women (Buss et al., 2007).

Although we acknowledge that many more factors are important, the factors are exhaustive and it was not feasible to include them all.

In the resilience study, we assessed risks and protective factors in the whole sample. As a consequence it is unclear if certain children indeed suffered from adversity that carry a markedly increased risk for development of psychopathology, which made it hard to quantify resilience in this study. Besides that, the environmental influences we measured in this study can be part of the same continuum instead of separate entities; in other words the same environmental experience can be a potential protective or a potential risk factor. Another weakness of this study is that we did not correct for multiple measurements.

In chapter 2 a review is presented of candidate genes which might contribute to PTSD. Although important, it only shows candidate genes which have been examined before. Furthermore genotypes can only be evaluated in the context of their environment. The G x E study described in chapter 4 certainly did not cover all genes, which results in a possible genetic bias: some variations remain hidden in the present investigation, such as gene-gene interactions or influences of other genotypes. Secondly, we need to be aware that genetic and environmental risk factors are not independent entities. Bad experiences are not randomly distributed in the population (Rutter, 1999). Individuals shape and select their own experiences determined by the cognitions and behaviour of individuals. For example, individuals who exhibit high levels of internalizing traits may experience relatively more stressful life events, which are partly genetically mediated (Silberg et al., 1999). Also parenting includes both genetic and environmental influences, as parents not only shape their children's upbringing but also pass on their genes (Rutter, 1999). At the same time children will have an influence on their environment (parents) as well (Rutter, 1999). For example the temperament of the child might influence the expression of genes in the mother, and as such influence the behaviour of the mother.
Another important limitation is the fact that a replication study for our findings is lacking. Our genetic findings are only based on one study and were not confirmed in another population. Further research is needed to prove these findings. Finally, the statistical approaches to study G x E interactions are complicated and not yet fully developed. There has been debate about the adequacy of the use of ANOVA models in detecting G x E interactions (Meaney, 2010; Wåhlsten, 1990).

In the studies of stress in-utero and stress early in life we did not examine ‘timing’ of sensitive periods. However, timing seems to be important. For example, there is compelling evidence for critical and sensitive periods in development. This suggests that some traits or skills are more readily acquired at certain stages of childhood than other traits (Knudsen et al., 2006). Davis and Sandman (2010) showed that high maternal cortisol in early pregnancy had a negative outcome on mental development at age one, while high cortisol late in gestation was associated with accelerated cognitive development and higher mental development at age one (Davis and Sandman, 2010). This highlights that stress later in pregnancy can even have positive effects. In conclusion, it is not only the exposure to stress in-utero but also the timing of exposure that appears to be relevant. In the studies we used only birth parameters (corrected for gestational age) as a reflection of the environment in-utero. As a consequence, we were not able to postulate further on sensitive periods. Of note, the finding that birth length was correlated with a higher IQ in our study in chapter 3 underscores that timing is indeed important for cognitive development, as birth length mainly increases in the second trimester. This midgestation phase of pregnancy is indeed known for development of cortical layers that participate in higher cognitive functions.

In the studies all ethnicities in Singapore and the Netherlands were included. However, for the genetic study as well as the study of the development of the resilience scale, data were only evaluated among Chinese subjects. It would be interesting to determine whether there are any differences among other ethnic groups in Singapore. Also, because the study was carried out among Chinese adolescents in Singapore, the extent of its generalizability as a measure of resilience in Chinese adolescents in other Asian countries is not known. These should be further investigated in future studies.

6. What’s next? Future studies...

We still have to learn if psychopathology can be explained by taking a life span approach, however, recent research shows strong evidence. This research has shown that early life, in-utero and in childhood, is a period of unique sensitivity that, in interaction with genotypes, has long lasting effects throughout life. However, the mechanisms for these effects remain almost as much a mystery today as a century ago. Research in the area has given us a lot of information, but also raised many new questions. This shows us that most of these interactions are still not well understood.

As development is complex and challenging to study, study models should be sophisticated enough to a good understand of what is going on ‘in real life’. As Albert Einstein formulated many years ago: “Everything should be as simple as possible, but not simpler”? This is reflected in ‘new science’, which uses multidirectional models instead of unidirectional ones, with growing emphasis on G x E interactions, epigenome-experience transactions and...
brain plasticity. These advances are based on the interconnectedness of genes and environment. Combination of behavioural science and physical science are needed to capture the complete processes underlying developmental change. As a consequence, interdisciplinary collaborations are required for developmental research.

Together with all the previous data in this area, hopefully our previous and planned studies will add to more evidence in the field of developmental psychopathology.

In the Singapore Cohort Study of the Risk factors for Myopia (SCORM) database we are still analyzing data to reveal more G x E interactions. As (early) stress has been associated with changes in the HPA axis, we are currently examining associations between birth weight and socio-emotional development of children in interaction with genotypes of candidate genes involved in the HPA-axis.

Moreover, a follow-up study with the SCORM population has recently started. The children included in this sample are now around 18 years old. In this follow-up study participants are asked to fill out questionnaires, such as the Youth Self Report, the Parental Bonding Instrument, the Parental Authority Questionnaire, the SYRESS Resilience scale and the Academic Expectations Stress Inventory (Ang and Huan, 2006). This study will inform us about the socio-emotional development of the children during adolescence and will add important data relating to parenting and academic stress factors, which are currently missing in the data of SCORM. With these data we may be able to assess if parenting styles modify the association between early life experiences and socio-emotional outcomes in children.

At the same time a study is examining the economic outcomes of SCORM. This is part of a larger worldwide project in which the International Healthy Start to Life Project (IHSLP) is included with Prof. Gluckman and his researchers as well as the team of Nobel laureate James Heckman, who developed technology of capability formation. They will examine the cost-effectiveness ‘to invest’ in early life of children in different developing as well as developed countries over the world. Genetics as well as many biological and social factors will be included in the model. This study, in which the economic costs (in dollars) of early life differences between countries will be made clear, will translate research into practical models for governments. They will also examine when it is more effective to intervene, during early growth versus later in childhood, by defining critical and sensitive periods for investment.

Furthermore, a large translational and clinical research (TCR) flagship program called Developmental Origins: Singapore (DevOS) has been launched to specifically assess the health problems that exist in Singaporeans, especially from pregnancy to infancy as well as adulthood (website: http://www.devos.sg/). The main study under DevOS is Singapore’s largest and most comprehensive birth cohort study “Growing Up in Singapore Towards Healthy Outcomes” (GUSTO) (website http://www.gusto.sg/). GUSTO is a long-term unique cohort study involving Singaporean mothers-to-be aimed at discovering effective prevention and early intervention strategies to reduce the burden of metabolic diseases in Asia and thus providing valuable information about the ‘Asian phenotype’. The cohort was completed by September 2010, in over a year, with 1234 eligible mothers who had signed up and 502 babies who have been safely delivered. Many measurements are used, inclusive regular early growth scans in-utero, DNA, MRI studies of newborns, as well as childhood environmental predictors of development and childhood health and growth and behaviour after birth. From this study an enormous amount of data will be provided to continue epigenetic studies examining associations and interactions between early growth,
genotypes and socio-emotional and cognitive outcomes in children. It will help to identify factors that may affect brain development and to create better early intervention programs for children who need them.

Finally, it would be important to collaborate with researchers over the world, to use data of other large birth cohort studies to replicate and compare outcomes, especially when genes are involved.

As described, most of our planned future studies show the integration of behavioural and physical science. Although this is in line with recent developments, for clinicians the importance of the inclusion of ‘soft science’ need to be underscored: as Greben has stated “….in times when the pendulum of psychiatric thinking swings more toward the biological and away from the psychological, it is essential to remind ourselves that helping people can never be divorced from listening to and talking with them” (Greben, 1992).