Stress, Vulnerability & Resilience

A Developmental Approach

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PhD SUMMARY

Stress, vulnerability and resilience, a developmental approach

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Background: The origins of mental disorders arise often in childhood. Early life is a period of unique sensitivity with long lasting effects on mental health. However, the mechanisms for these effects remain unclear.

Objective: This thesis describes a variety of studies using a developmental framework to promote greater understanding of the influence of nature (genotypes) and nurture (e.g., environmental risk and protective factors) on outcomes later in childhood.

Method: The aim of this thesis is to investigate gene and environmental influences on behavioural, emotional, and cognitive outcomes in different samples from the Netherlands and Singapore, most derived from the general population. We assessed early life influences from a neurobiological, social, and a psychological perspective by using a biopsychosocial framework.

Results: Our studies support the hypothesis that all experiences during life, including early experiences *in utero*, will influence the expression of genes and in the end the mental health of individuals. However, genotypes influencing stress responses are found to be "plastic," which implies that they can be modulated by environmental experiences during life. In line with this, patterns of resilience are found to be context-dependent too.

Conclusions: The model of "epigenetic programming" suggests the predictive power of the environment *in utero* and early childhood on mental health later in life. This association is probably determined by a neurodevelopmental pathway with individual differences in neural and endocrine responses to stress.

Keywords: *Stress disorders*; *genes*; *genotypes*; *resilience*; *cognition*; *behaviour*; *child development*

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During the last 50 years there have been dramatic changes in our understanding of mental disorders (Rutter, 2010; Rutter & Smith, 1995). One such change is the awareness of the prevalence and impact of psychiatric disorders in childhood (Costello, Foley, & Angold, 2006; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003b). Early life is a period of unique sensitivity with long lasting effects on mental health. However, the mechanisms for these effects remain unclear.

Biological and environmental factors will naturally be involved. The dynamic interaction between genotypes and the environment is called gene × environment interaction (G × E interaction). The G × E interaction is present when the effect of genotype on the development of psychopathology depends on the level of exposure to an environmental factor (Belsky & Pluess, 2009; Meaney, 2010; Rutter et al., 1997). 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.

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Environmental influences include demanding stressful events from *in utero* to adulthood. Stressful events will have an effect on physiological stress systems. There are two different important physiological stress systems; the sympathetic adrenergic medullary axis (SAM; Henry, 1992; Porges, 1991; Ursin & Olff, 1993), and the hypothalamic pituitary adrenal axis (HPA; Harbuz & Lightman, 1992). Although stress reactions can be useful to adapt to situations, prolonged or severe stress reactions can be maladaptive, and can lead to symptoms of posttraumatic stress, depression, and/or can have an influence on cognitive functioning (Christopher, 2004; Olff, Langeland, & Gersons, 2005; Peleg & Shalev, 2006; Raison & Miller, 2003; Yehuda, 2002).

Individuals are considered resilient when they adapt well, without developing psychopathology or health problems despite experiencing adversity. Resilience is defined contextual (Rutter, 2006a). Environmental factors that lead to resilience in one context may not lead to resilience in other circumstances. 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, Mezzacappa, & Beardslee, 2003; Rutter, 2006a, 2006b).

There are important differences between cultures in social context (such as self-development and individualisation in western countries, while in Asia the emphasis is on strong family bonding and interdependency) and in the perception of stressors. As a consequence there is increasing awareness to incorporate culture and diversity into the study of stress and resilience (Arrington & Wilson, 2000; Ungar, 2006, 2008).

The biopsychosocial model used in this thesis covers a timeline from preconception to adolescence (see model 1). This model describes the interactions between environment and genotypes of the parents, the foetus, 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. These 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. (Conger, Ge, Elder, Lorenz, & Simons, 1994; Costello, Compton, Keeler, & Angold, 2003a). 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—it's resilience (Fig. 1).

In this thesis a developmental approach was used to understand how nature (genotypes) and nurture (e.g., environmental risk or protective factors) interact to determine developmental outcomes. The influences of stress *in utero* and during early life in interaction with genotypes on socio-emotional and cognitive outcomes are studied in different age groups and of different cultures. Additionally a "resilience questionnaire" was developed for children in an Asian population.

The emphasis is on studies done mainly in a general population to examine the impact of (early) life influences in the majority of children. This is in addition to previous developmental studies that used to focus on children with rare diseases or children living in extreme or aversive situations.

Summary of the results of the studies

The results of our studies are included in model 2 (Fig. 2).

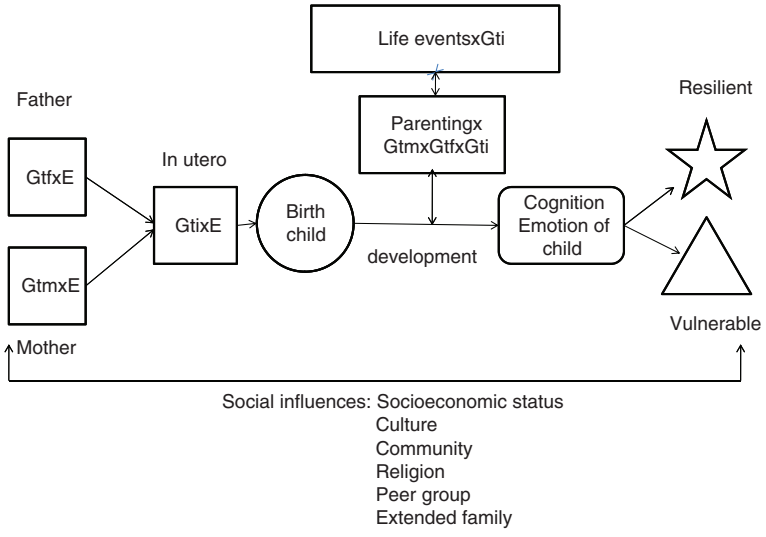

Fig. 1. Model 1.

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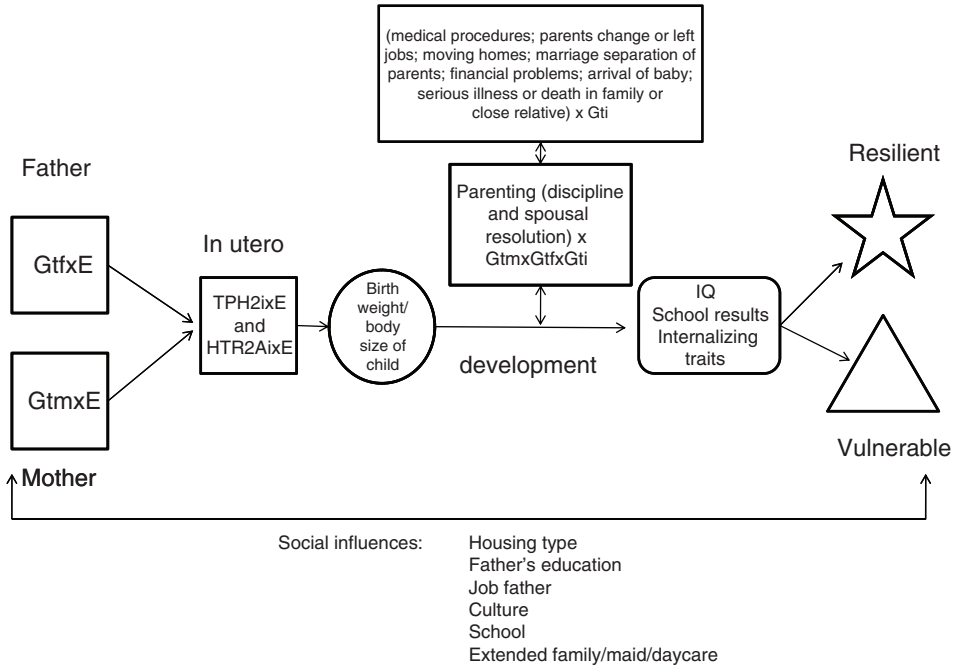

Fig. 2. Model 2.

Studies in genetic vulnerabilities

In chapter 2 a review is given of candidate genes, which in interaction with environmental factors are associated with post-traumatic stress disorder (PTSD). It shows that—in contrast to many other psychiatric disorders—no extensive genetic studies have been performed on PTSD. Key candidate genes in the serotonin, dopamine, glucocorticoid, gamma aminobutyric acid (GABA), apolipoprotein, brain-derived neurotrophic factor, and neuropeptide Y are discussed. The results indicate that the serotonin transporter gene possibly plays a role in the degree of response to stressful events, in particular, in the sensitivity of individuals to the depressogenic effects of stressful life events. The studies on other candidate genes show inconsistent results, probably due to methodological shortcomings. G × E studies will be needed to fully understand the role of these genes in different environments.

In chapter 4 we describe a G × E study done in a sample of 545 healthy Chinese children from age 8 to 12, recruited from three different schools in Singapore. In this study the influence of birth weight corrected for gestational age (as a reflection of the environment *in utero*) in interaction with variation of genes involved in the serotonergic system on internalising traits is examined. Gestational age was calculated from mothers' last menstrual date and confirmed by foetus' crown rump length during the first trimester ultrasonography. Birth weight data were obtained from medical record booklets containing data recorded at parturition. Internalising traits were measured with the Child Behaviour Check List (CBCL). After correction for multiple confounders with a total of nine examined single nucleotide polymorphisms (SNPs), significant interactions are found between birth weight (corrected for gestational age) and two SNPs of the *TPH2* gene, which are in high linkage disequilibrium with each other (rs2171363, $p = .008$; rs7305115, $p = .007$) and two SNPs of the *HTR2A* gene (rs2770304, $p = .001$; rs6313, $p = .026$). The CC genotype of *TPH2* rs2171363, GG genotype of *TPH2* rs7305115, CC genotype of *HTR2A* rs2770304, and CC genotype of *HTR2A* rs6313 are associated with reduced internalising scores in children born in the quartile above the mid-point within the normal range for birth weight. In conclusion, this study shows that the effects of foetal growth on socio-emotional traits that associate with affective disorders are modulated by genotypes of the *TPH2* and *HTR2A* genes, suggesting that variation in genes involved in the serotonergic system determine the influence of foetal growth. Second, the results reveal a foetal growth × genotype interaction effect that results in significantly reduced levels of internalising scores associated with birth weight lying above the average within the normal range. Third, and perhaps most strikingly, three of the four genotypes that interact with birth weight to reduce internalising scores are those that in adult populations associate with an increased risk for affective illness. Strengths of this study include the large sample of Chinese children, selected polymorphisms with evidence of associations with affective disorders, and exclusion of important confounders such as maternal smoking. Limitations include missing other possible restraints of foetal growth because they were not measured (e.g., use

of alcohol), the reliance on parental report, and the possibility of undetected variations of gene–gene interactions.

Studies of in utero influences

Studies on (very) low birth weight and premature children showed that Intelligence Quotient (IQ) is consistently correlated with birth weight. However, within the normal birth size range, this association has been less conclusive. In chapter 3 we describe a cohort study of 1,979 Singaporean children, who attended three different mainstream schools, which examines the influence of the environment *in utero* (reflected by birth weight corrected for gestational age) on IQ at age 8 to 12 years. Birth data were abstracted from children's medical charts. The IQ was measured using the Raven's Progressive Matrices. The results show that for every 1 kg increase in body weight; the model predicts a 2.19 ($p = .007$) increase in IQ score; for every 1 cm increase in length an increase of 0.49 points ($p < .001$) in IQ score and for every 1 cm increase in head circumference an increase of 0.62 ($p = .003$) in IQ score. These associations persist even after adjustment for multiple confounders, and after exclusion of premature children and children with extreme weights and head circumferences. An analysis of a sub-sample of siblings shows that the taller sibling (at birth) has significantly higher IQs than the shorter sibling as well. In sum, the results show that improved foetal growth predicts increased IQ at school age across the entire population. The major strengths of this study are the use of multiple birth parameters as surrogates of foetal growth, the large sample size with high follow-up rate, the sibship analyses to exclude important family environmental factors, and the use of a well-validated IQ test minimising the effects of language and culture. Limitations include possible selection biases due to loss to follow-up, missing birth parameter data, and residual confounding as some other covariates of interest were not measured.

The study in chapter 4 shows the association between the early environment *in utero* in interaction with genotypes of the serotonergic system on socio-emotional development. This study is described in more detail under "studies in genetic influences." Although the association between birth weight and IQ shows a linear trend, the association between birth weight and internalising traits shows a non-linear relationship, modulated by genotypes.

Study in stress during early childhood

Children react differently to a stressor such as a medical procedure. Prospective studies, which examine predictive factors for differences in stress responses to a surgery, are rare. In chapter 5 a cohort study is described in which the influence of a standard medical procedure (adenoidectomy or adenotonsillectomy—A&ATE) on the stress response is performed in a Dutch sample of 43 children of age 2 to 7 years. This study reports child behaviour and neurophysiologic characteristics in young children before and after surgery, to investigate individual differences in the stress response measured in a prospective way. Four weeks before surgery parents completed questionnaires on temperamental traits of their child Emotionality, Adaptability, Sociability (EAS) and the CBCL (measuring behaviour and emotion). Baseline neurophysiologic measurements, cortisol (measured in saliva) and respiratory sinus arrhythmia (RSA, derived from heart rate variability measured with an electrocardiogram) were performed 4 weeks before surgery. Directly after surgery and 6 weeks post-surgery cortisol and RSA measurements were repeated to measure the neurophysiologic stress responses. Six weeks post-surgery the child version of the Impact of Event Scale and the Child Sleep Habit Questionnaire were given to parents to measure, respectively, post-traumatic stress symptoms and sleep problems, and the CBCL was repeated to measure behaviour and emotional changes. The results show that A&ATE is not very stressful for most children. It seems to be a helpful procedure to reduce pre-existing behavioural and emotional and/or sleep problems in, respectively, 75% and 68% of the children, especially in boys. Post-traumatic stress symptoms are rare. In contradiction to earlier findings there is no association between shyness and the stress response. Our findings do not show a predictive value for neurophysiologic parameters. However, more research will be needed to examine the role of emotional temperament, which is associated with more behavioural problems before surgery ($r = .53$, $P = .02$), after surgery ($r = .38$, $P < .000$), lower cortisol directly after surgery ($r = -.49$, $P = .05$), and lower RSA at follow-up ($r = -.33$, $P = .06$). More research is also needed to explore the role of gender. Girls and boys show different outcomes in this study, with a larger benefit of A&ATE for boys, however the number of girls was small.

Strengths of this study include the prospective design and the inclusion of physiologic measures, which allow direct measurements of emotional states of children, aside from self-rating parental psychological questionnaires. Limitations of this study include missing data reducing the sample size and the possibility of confounders, as we did not include other important covariates such as the care-giving context.

Studies in resilience

Resilience is often studied in children living under extreme circumstances or having illnesses. However, empirical understanding of the influence of risks and protective factors in a large normative population is important in improving mental health and psychosocial competence in children. In chapter 6 we describe a cohort study of 2,139 Singaporean children, aged 6 to 12 years, recruited from 18 primary schools. The study was designed to examine relationships between common risks and protective factors in childhood with socio-emotional

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development and academic performance at age 7 to 12. A variety of questionnaires were used: IQ was measured with the Raven's Progressive Matrices, academic results were based on school results given by the school, and behavioural and emotional problems were measured with the CBCL parental report and the Teacher Rating Form (TRF) to obtain teacher-reported information. The child's adaptive functioning at school was measured with a survey by teachers in terms of his/her ability to work, to behave, to learn, and to be happy in school, all compared to other pupils of the same age. Variables representing protective and risk factors were created from demographic data about the child and family, derived from a questionnaire based on the Family and Household Questionnaire 75-item questionnaire related to family functioning and derived from a list of life events, all provided by mother. A multivariate modelling (SEM) was performed to construct a heuristic model examining the impact of protective factors and risks on children's socio-emotional development and adaptive functioning and academic performance.

The results show that some protective factors (intelligence, father's education and occupation) are strongly associated with fewer emotional and behavioural problems in children ($\beta = -.242$, $T = -2.56$) and a lesser likelihood of poor adaptive functioning and lower academic scores ($\beta = -.55$, $T = -7.91$). At the same time it shows that some risk factors (negative spousal conflict resolution, negative methods of discipline, chronic health problems, negative life events, and developmental delay) are associated with more emotional and behavioural problems ($\beta = .487$, $T = 8.12$), without showing an association with academic results. These findings reinforce the importance of both positive resilience building focusing on assets and resources as well as alleviating risks and adversities.

Strengths of this study include the involvement of adversities as well as protective factors, the large sample size, and data from different sources (parents, teachers, school reports). Limitations include the fact that only a selection of factors that may influence mental health and academic outcome were measured, the low participation rate, the differences in socio-economic status between the included and excluded sample, and the lack of known psychometric properties of used instruments in Asia.

Multicultural resilience research has revealed that patterns of resilience are context-dependent. This suggests that trans-cultural use of standardised resilience measures developed in the Europe and America, and even for similar ethnic groups in different parts of Asia, is theoretically unsound. For those that have been validated cross-culturally, the findings indicate that the understanding of the construct requires some modification according to the culture in which it is measured. To date, no measure of resilience has been developed for use with adolescents within the cultural context of Singapore. In chapter 7 the development and validation of the Singapore Youth Resilience Scale (SYRESS) is described. The development is based on an exhaustive review of the literature; review of existing domains and items and addition of new domains and items by a focus group of researchers, child psychologists, and psychiatrists with local and international content expertise; and additional feedback and contributions obtained from an external expert panel with similar content expertise. It was ensured that the domains and items were comprehensive as well as culturally relevant. To examine the factor structure of SYRESS an Explanatory Factor Analysis was performed, which resulted in a 50-item scale reflecting 10 domains of resilience, which accounted for 63.4% of the variance in the SYRESS scores. The 50-item SYRESS demonstrates sound psychometric properties, with good internal consistency (Cronbach's alpha 0.95), and test-retest reliability ($r = 0.82$). The SYRESS strongly correlates with another measure of resilience, the Connor-Davidson Resilience Scale (CD-RISC) ($r = 0.88$), and also relates to higher levels of quality of life and wellbeing, as measured with the WHOQOL-BREF ($r = 0.57$) and lower psychiatric morbidity, as measured with the GHQ-28 ($r = -0.33$). Factor analyses showed that the hybrid SYRESS scale encompasses all the factors represented separately by other existing scales, and hierarchical regression analyses show that the SYRESS significantly contributes additional variance to the prediction of the WHOQOL-BREF and GHQ-28 scores over and above that contributed by CD-RISC alone. Limitations include the fact that analyses were restricted to Chinese subjects only, due to the low response rate of Malay and Indian students.

General discussion

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 1 year of age seem to programme offspring growth and metabolic pathways, altering lifelong susceptibility to diseases later in life (Bale et al., 2010; Barker 1998, 2007; Fogel, 2003; Gluckman and Hanson, 2005; Gluckman, Hanson, Morton, & Pinal, 2005; Gluckman & Hanson, 2006; Rutter, 2006b; Rutter, Moffitt, & Caspi, 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 & Martyn, 2004; van den Hove, Kenis, Steinbusch, Blanco, & Prickaerts, 2010; Wiles, Peters, Leon, & Lewis, 2005). Hence, an optimal environment *in utero* (in interaction with the genotype of the foetus) is important for optimal

development, not only physically but also psychologically (Gluckman et al., 2005).

The stress diathesis model (Francis, Caldji, Champagne, Plotsky, & Meaney, 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, Szyf, & Seckl, 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 signalling in the key brain areas (Kajantie & Räikkönen, 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 & Hanson, 2004; Gluckman, Hanson, & Beedle, 2007).

Our studies in *in utero* development showed an effect of foetal growth on IQ, as well as on socio-emotional traits associated with affective disorders. Interestingly, IQ has been positively related to health later in life (Batty, Deary, & Gottfredson, 2007). This suggests that one explanation of the association between foetal 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. In chapter 4 children with a birth weight (corrected for gestational age) just above the mean had lower internalising scores, modulated by genes involved in the serotonergic system (*TPH2*, *HTR2A*). Genotyptic 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 foetal 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. This is in line with findings of animal studies. Fish et al. (2004) clearly demonstrated the influence of maternal care on HPA function by epigenetic programming of the glucocorticoid receptor expression, increasing or decreasing the impact of sequence variation. The hypothesis about change in activity of genes by experiences during life, without alteration of DNA, is seen as "epigenetic programming" (Meaney & Szyf, 2005) and has been shown in previous studies (Caspi et al., 2003; Gotlib, Joormann, Minor, & Hallmayer, 2008; McGowan et al., 2009).

Stress during life, resilience, and cultural influences

In chapter 5 we describe a study that 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 (Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010). This effect could explain our finding in chapter 5 that high stress reactivity measured by RSA and cortisol was not a predictor, in it self, 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 characterised 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 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

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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 and not the academic capacities. These findings parallel those of the effects of poverty in children (Hackman, Farah, & Meaney, 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 martial conflict and parenting problems such as those described above. Parenting mediates the effects of poverty of socio-emotional but not academic outcomes (Hackman et al., 2010).

Interestingly, in this study described in chapter 6 we found some differences in risk factors with earlier findings from the other studies done in European countries. For example, family structure and surrogate care giving were relatively less important risk factors than in Europe and America. This might be related to differences in culture, as Singaporean children are more often raised with surrogate care giving, by living-in grandparents and/or domestic helpers, while in America and Europe parents more often use day care 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, we should not over-emphasise universal mechanisms and determinants of resilience as local cultural influences cannot be neglected. In chapter 7 we developed a resilience scale for the Singaporean population, in addition to the existing resilience scales developed in America and Europe. The SYRESS was found to be a validated tool and a more comprehensive measure of resilience in adolescents than some existing scales. As a hybrid scale, the SYRESS has the advantage of encompassing all the underlying mechanisms measured separately by other regular scales but remaining a relatively short 50-item scale, which is easy to administer and score.

Conclusions

Our studies support the hypothesis that all experiences during life, including early experiences *in utero*, will influence the expression of genes and, in the end, the socio-emotional and cognitive development later in life. This model of "epigenetic programming" suggests the predictive power of the environment *in utero* and early childhood on mental health later in life. The stress diathesis model proposes that this association is probably determined by a neurodevelopmental pathway with individual differences in neural and endocrine responses to stress. However, genotypes influencing the neural and endocrine stress responses are "plastic," which implies that they can be modulated by environmental influences during life.

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. A developmental approach is useful to explore those influences.

Clinical implications

Our studies underscore that a life span strategy will help to emphasise multiple factors during life, which influence the development of the child and help to diagnose problems. The impact of prenatal adversity on neural development can be modulated by environmental factors later in life. This has implications for targeting clinical treatment programmes such as parent-child interventions. Although we did not focus on parenting in most of 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 (Bakermans-Kranenburg, van Ijzendoorn, Mesman, Alink, & Juffer, 2008; Fish et al., 2004; Lupien, King, Meaney, & McEwen, 2000).

Developmental studies are also important for education of the general public and for policy makers. Based on evidence of these studies programmes for prevention can be developed. For example, optimalisation of foetal and maternal care during pregnancies can have a significant positive impact on future health and well-being of offspring. Other examples are use of remedial teaching and resilience building programmes for youth (Fisher, Gunnar, Chamberlain & Reid, 2000; Olds et al., 2002).

Notably, these clinical as well as prevention programmes need to be evaluated in different environments and cultures.

Future perspectives

As development is complex and challenging to study, study models should be sophisticated enough to be a good understand of what is going on "in real life." This is reflected in "new science," which uses multidirectional

models instead of unidirectional ones, with growing emphasis on G × 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 in developmental research. It also would be important to collaborate with researchers all over the world to use data of other large birth cohort studies to replicate and compare outcomes, especially when genes are involved.

Conflict of interest and funding

The author declares no conflict of interest.

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