Stress, vulnerability and resilience: a developmental approach
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Summary

“Print” by Lucas Lentzher, 3 months old
1. Background

This thesis describes a variety of studies using a developmental framework to promote greater understanding of the interaction between genotypes and environmental influences on outcomes later in childhood. We assessed early life influences from a neurobiological, social and a psychological perspective by using a biopsychosocial framework described in chapter 1.

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. Biological and environmental factors will naturally be involved. Environmental influences include demanding stressful events from in-utero to adulthood. Individuals are considered resilient when they adapt well, without developing psychopathology or health problems despite experiencing adversity. Although stress reactions can be useful to adapt to situations, prolonged or severe stress reactions can be maladaptive. For example, prolonged stress responses can lead to symptoms of posttraumatic stress and depression, and/or can have an influence on cognitive functioning. During stress, two different physiological stress systems are involved; the sympathetic adrenergic medullary axis (SAM) and the hypothalamic pituitary adrenal axis (HPA).

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.

2. Research questions

With our studies we tried to answer the following questions:
1. What are common candidate genes which, in interaction with environmental influences, have been associated with prolonged stress reactions leading to Posttraumatic Stress Disorder?
2. What is the influence of the interaction between variation in genes involved in the serotonergic system and the environment in-utero (reflected in birth weight corrected for gestational age) on internalizing traits in children (measured with the Child Behavior Checklist, CBCL) at age 8 to 12 years?
3. What is the influence of the early environment in-utero (reflected in weight, length and head circumference of the newborn at birth, corrected for gestational age) on IQ in children (measured with the Raven’s Progressive Matrices) at age 8 to 12 years?
4. What is the impact of a standard surgery early in life on the stress response of young children? Are temperamental traits or neurophysiologic characteristics of the child predictors of the stress response?
5. What is the effect of common risks and protective factors during childhood on the outcome of children in terms of socio-emotional development (measured with the CBCL and TRF) and academic outcomes (school results and adaptive functioning) at age 8 to 12 years old?
6. What is the need for developing a comprehensive cultural-sensitive resilience scale and what are the similarities and differences between resilience scales originating in Europe and the USA, and Asia?
3. Summary of the results of the studies

3.1. Studies in genetic vulnerabilities

In chapter 2 a review is given of candidate genes, which in interaction with environmental factors, are associated with Posttraumatic Stress Disorder (PTSD). This study was the first study to give a full overview of candidate genes related to PTSD found with a literature search in Medline, Embase and Web of Science. 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, GABA, apolipoprotein, brain-derived neurotrophic factor and neuropeptide Y systems 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. Gene x environmental (G x E) studies will be needed to fully understand the role of these genes in different environments.

In chapter 4 we describe a G x E study done in a sample of 545 healthy Chinese children from age 8 to 12, recruited from 3 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 internalizing traits is examined. Gestational age was calculated from mothers’ last menstrual date and confirmed by fetus’ crown rump length during the first trimester ultrasonography. Birth weight data were obtained from medical record booklets containing data recorded at parturition. Internalizing traits were measured with the Child Behavior Checklist (CBCL). After correction for multiple confounders, of a total of 9 examined single nucleotide polymorphisms (SNPs), significant interactions are found between birth weight (corrected for gestational age) and 2 SNPs of the TPH2 gene, which are in high linkage disequilibrium with each other (rs2171363, P = 0.008; rs7305115, P = 0.007), and 2 SNPs of the HTR2A gene (rs2770304, P = 0.001; rs6313, P = 0.020). The CC genotype of TPH2 rs2171363, GG genotype of TPH2 rs7305115, CC genotype of HTR2A rs2770304 and CC genotype of HTR2A rs6313 were associated with reduced internalizing 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 fetal 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 fetal growth. Second, the results reveal a fetal growth x genotype interaction effect that results in significantly reduced levels of internalizing scores associated with birth weight lying above the average within the normal range. Third, and perhaps most strikingly, 3 of the 4 genotypes that interact with birth weight to reduce internalizing scores are those that in adult populations associate with an increased risk for affective illness. These findings suggest that genetic variants that statistically associate with an increased risk for affective illness might act to enhance sensitivity to environmental context, thus explaining bi-directional outcomes. These findings are consistent with emerging ideas (e.g. Boyce and colleagues) suggesting that effects of such genomic variants may influence environmental sensitivity resulting in context-specific developmental outcomes. 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 out other possible restraints of fetal 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.

3.2. 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. Population-based studies with large sample sizes are rare, primarily conducted in European-derived populations, and sometimes only done in male participants.

In chapter 3 we describe a cohort study of 1979 Singaporean children, who attended 3 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. 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 = 0.007) increase in IQ score; for every 1 cm increase in length an increase of 0.49 points (P < 0.001) in IQ score and for every 1 cm increase in head circumference an increase of 0.62 (P = 0.003) 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 fetal growth predicts increased IQ at school age across the entire population. The implications are important as such findings emphasize the importance of prevention of not merely conditions that severely constrain fetal growth, but rather the entire range of factors that influence maternal-fetal health. The major strengths of this study are the use of multiple birth parameters as surrogates of fetal 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, minimizing 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 internalizing traits shows a non-linear relationship, modulated by genotypes.

3.3. 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 prospective 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. It was hypothesized
that temperamental traits and neurophysiologic characteristics of the child have a predictive value on the outcome after A&ATE. 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 (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 electrocardiography) 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 posttraumatic 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. Posttraumatic 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 temperance, which is associated with more behavioural problems before surgery ($r = 0.53$, $P = 0.02$), after surgery ($r = 0.38$, $P < 0.000$), lower cortisol directly after surgery ($r = -0.49$, $P = 0.05$) and lower RSA at follow-up ($r = -0.33$, $P = 0.06$). 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 caregiving context.

3.4. Studies in resilience

Resilience is often studied in children living under extreme circumstances or having illnesses. However, it is not easy to generalize the findings of children under extreme circumstances to the general population, although all children will face adversities during their development. Furthermore, studies in Asia are rare and many studies do not include protective factors. 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 2139 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 development and academic performance at age 8 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 used in the Ontario Child Health Study, 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 ($\beta = -0.24, T = -2.56$) and a lesser likelihood of poor adaptive functioning and lower academic scores ($\beta = -0.55, T = -7.91$). 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 ($\beta = 0.49, T = 8.12$), 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 which may influence mental health and academic outcome were measured, the low participation rate, the differences in socioeconomic 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 multiple conceptualisations of resilience are used worldwide, and that patterns of resilience are context-dependent. This suggests that existing resilience scales may not adequately represent all aspects of resilience and that trans-cultural use of standardized resilience measures developed in Europe and the USA, and even for similar ethnic groups in different parts of Asia, is theoretically unsound. Indeed, 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 Chinese 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. The SYRESS included 50 items reflecting 10 domains of resilience; perseverance and commitment, positive self-image and optimism, relationship and social support, humour and positive thinking, emotional regulation, spirituality and faith, personal confidence and responsibility, personal control, flexibility, and positive coping. A test-retest study was done, as well as association studies with other resilience and well-being questionnaires. The results show that the SYRESS has sound psychometric properties, with good internal consistency (Cronbach's alpha 0.95) and test-retest reliability ($r = 0.82$), and convergent validity with
the Connor-Davidson Resilience Scale, WHOQOL-BREF quality of life, and GHQ-28 psychological morbidity. Factor analysis revealed a 10-factor structure for the SYRESS (total variance of 63.4%), and hierarchical analyses showed that the SYRESS significantly contributed additional variance to the prediction of the WHOQOL-BREF and GHQ-28 scores over that contributed by CD-RISC alone, suggesting that the SYRESS is a more comprehensive measure. Limitations include the fact that analyses were restricted to Chinese subjects only, due to the low response rate of Malay and Indian students.

4. Answers to the research questions

1. What are common candidate genes which, in interaction with environmental influences, have been associated with prolonged stress reactions leading to Posttraumatic Stress Disorder?
   Genotypes involved in the serotonin, dopamine, glucocorticoid, GABA, apolipoprotein, brain-derived neurotrophic factor and neuropeptide Y system, in interaction with environmental events, have been associated with Posttraumatic Stress Disorder worldwide. However, results are inconsistent, and G x E studies will be needed to fully understand the role of these genes in different environments.

2. What is the influence of the interaction between variation of genes involved in the serotonergic system and the environment in-utero (reflected in birth weight corrected for gestational age) on internalizing traits in children (measured with the Child Behavior Checklist, CBCL) at age 8 to 12 years?
   The effects of fetal growth on internalizing traits are modulated by genotypes of the TPH2 and HTR2A gene, with a non linear fetal growth x genotype interaction effect that results in significantly reduced levels of internalizing scores for children with a birth weight lying above the average birth weight in Singapore.

3. What is the influence of the early environment in-utero (reflected in weight, length and head circumference of the newborn at birth, corrected for gestational age) on IQ in children (measured with the Raven's Progressive Matrices) at age 8 to 12 years?
   Improved fetal growth predicts increased IQ at school age across the entire population. It shows a linear association between birth weight, birth length and head circumference at birth and IQ scores in children at age 8 to 12 years old on the Raven's Progressive Matrices in Singapore.

4. What is the impact of a standard surgery early in life on the stress response of young children? Are temperamental traits or neurophysiologic characteristics of the child predictors of the stress response?
   A standard Ear Nose and Throat surgery is for most Dutch children not very stressful and can even be helpful to reduce pre-existing behavioural and emotional and/or sleep problems. Temperamental traits and neurophysiologic characteristics are not predictive of the stress response, although more research is needed to examine the role of children with an emotional temperament.
5. What is the effect of common risks and protective factors during childhood on the outcome of children in terms of socio-emotional development (measured with the CBCL and TRF) and academic outcomes (school results and adaptive functioning) at age 8 to 12 years old?

Some protective factors (intelligence, father’s education and occupation) are strongly associated with fewer emotional and behavioural problems in children ($\beta = -0.24$, $T = -2.56$) and a lesser likelihood of poor adaptive functioning and lower academic scores ($\beta = -0.55$, $T = -7.91$), while risk factors (negative spousal conflict resolution, negative methods of discipline, chronic health problems, negative life events and developmental delay) show a strong positive relationship with emotional and behavioural problems ($\beta = 0.49$, $T = 8.12$), but have no influence on academic results in Singapore.

6. What is the need for developing a comprehensive cultural-sensitive resilience scale and what are the similarities and differences between resilience scales originating in Europe and the USA, and Asia?

Multicultural resilience research has revealed that multiple conceptualisations of resilience have been described worldwide and that patterns of resilience are context-dependent. To date, no measure of resilience has been developed for adolescents within the cultural context of Singapore. In chapter 7, the development of the Singapore Youth Resilience Scale (SYRESS) is discussed. Although cultural items have been added to this scale, the developed SYRESS encompasses a set of underlying variables that appears consistent with universal determinants of resilience, like perseverance and commitment, positive self-image and optimism, relationship and social support, humour and positive thinking, emotional regulation, spirituality and faith, personal confidence and responsibility, personal control, flexibility, and positive coping. The SYRESS showed a better prediction of scores on quality of life and general health questionnaires than an existing resilience scale of the USA. This suggests that the SYRESS may be a more comprehensive measure, that is more useful in a Singaporean population.

5. 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.

6. Clinical implications

Our studies underscore the need for a life span strategy. This will help to emphasize 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 pro.
grams, such as parent-child interventions. Developmental studies are also important for education of the general public and for policymakers. Based on evidence of these studies, programs for prevention can be developed, such as optimization of fetal and maternal care during pregnancies, remedial teaching, and resilience building. Notably, these clinical as well as prevention programs need to be evaluated in different environments and cultures.

7. Future research

The theory of epigenetic programming with effects on adult (mental) health underscores the need to focus on multidirectional research models in the future, with growing emphasis on G x E interactions 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. Continuing studies in this area are planned for the coming years.