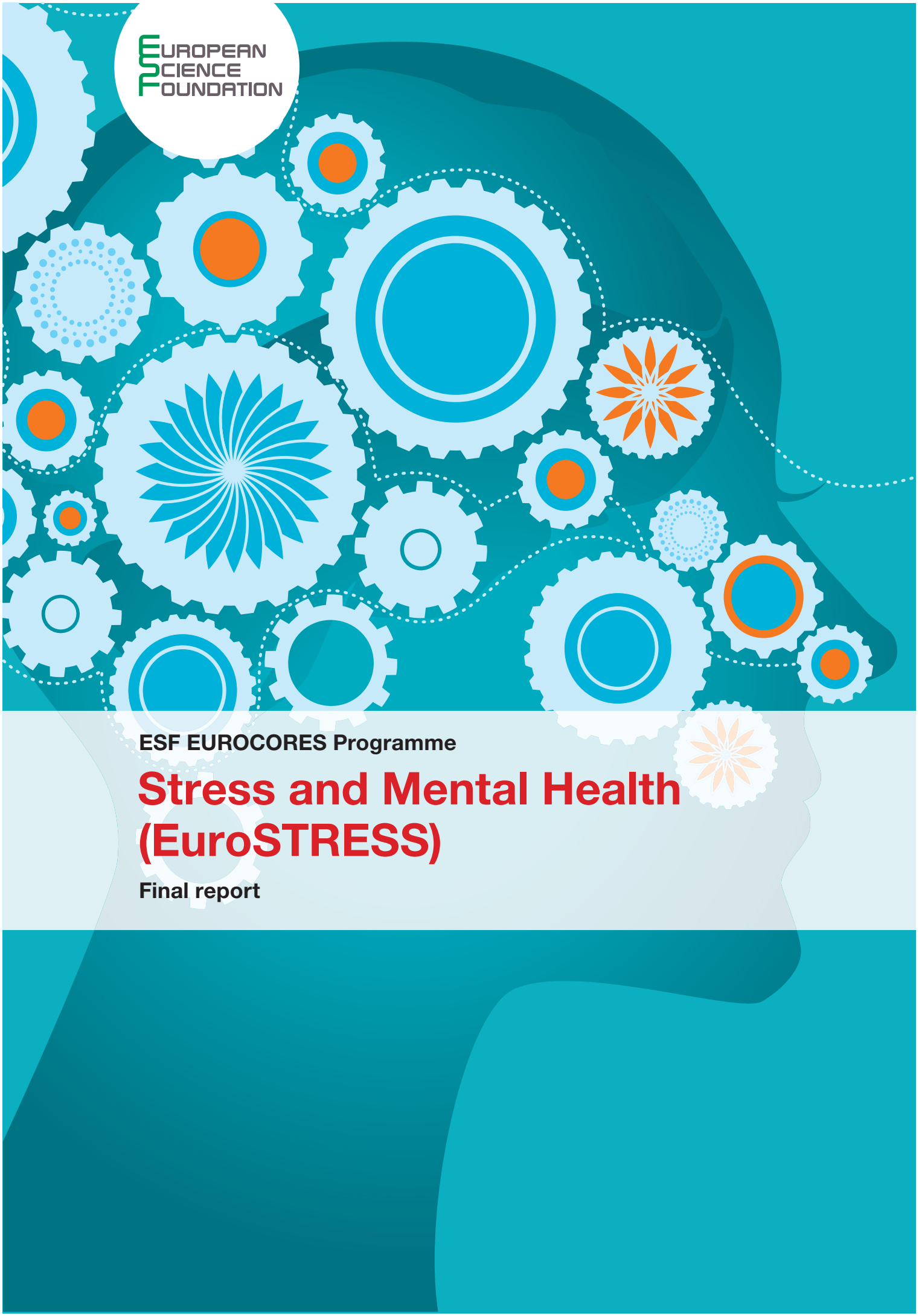

ESF EUROCORES Programme

Stress and Mental Health (EuroSTRESS)

Final report

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Until the end of 2008, scientific coordination and networking was funded through the EC FP6 Programme, under contract no. ERASCT- 2003-980409. As of 2009, the national organisations support all aspects including scientific coordination, networking and research funding.

www.esf.org/eurostress

Editors
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Dr Lars V. Kristiansen, Science Officer
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Abbreviations used
Arc: Activity-regulated cytoskeleton associated protein
ANS: Autonomous nervous system
BDNF: Brain derived neurotrophic factor
CNS: Central nervous system
CORT: Cortisol/corticosterone
CRP: Collaborative Research Project
EC FP6: The European Commission's Sixth Framework Programme
ERP: Event-related brain potential
ESF: European Science Foundation
EUROCORES: European Collaborative Research
GR: Glucocorticoid receptors
GWAS: Genome-wide association study
HPA: Hypothalamo-pituitary-adrenocortical
IP: Individual Project
MR: Mineralocorticoid receptors
PI: Principal Investigator
PTSD: Post-traumatic stress disorder

Contents

Introduction

Following the successful 2006 theme proposal on stress and mental health, the EuroSTRESS EUROCORES Programme was launched by ESF in 2008. The theme proposal was evaluated by peers as highly important and timely and similarly was highly rated by the Science Advisory Board and the ESF Governing Council. Consequently, the theme call proposal, which was overall considered to represent an excellent example of a truly multi-disciplinary framework that would provide European research in the area of stress-related psychiatric conditions with a unique possibility to address questions that would not be possible at the individual laboratory level or even at the national level, was recommended for funding by national ESF member organisations.

Stress and stress-related disorders such as depression and psychosis and post-traumatic stress disorder (PTSD) have often been linked to psychosocial factors that are intimately connected to the way modern society impinges on our daily life. For the affected individual, the burden that is associated with stress and its related conditions, including loss of life quality and stigmatisation, are evident. However, these disorders also represent a huge financial and social burden for wider society.

As our knowledge about stress and mental disorders has accumulated over the past decades, it is clear that in addition to more traditional risk factors, additional elements such as genetic background and early life events play a central role in predisposing an individual to these complex disorders. In view of technological advances that have emerged over the last decade and significantly pushed the limits for what is possible with disciplines such as neuroimaging, genomic analysis and genetic marker studies, it is now highly propitious to attempt to gain further insight into the etiology and pathophysiology of the severe mental conditions that are particularly sensitive to gene–environment interactions such as stress and stress-related disorders.

The present report results from a multiannual multidisciplinary European collaborative research programme (EUROCORES) that has specifically focused on stress and mental health (EuroSTRESS). The objective of this programme was, through a formal collaboration of leading research groups, to advance our understanding of how early life experiences, genetic background and repeated traumatic events in adulthood may predispose to development of specific psychiatric disorders including stress.

The overarching objective for the EuroSTRESS programme was to increase our knowledge about the basic mechanisms of stress-related mental disorders with the aim of using this knowledge for the development of new treatment strategies and the actual prevention of these types of disorders. This report gives a thorough overview of the collaborative research projects (CRPs) including their composition and individual foci. Further, it describes the activities that were undertaken to promote exchange and collaboration within and across CRPs as well as provides a showcase of specific outputs from the programme.

1.
Governing Bodies

The quality of the EUROCORES Programme EuroSTRESS was ensured by the following committees.

EuroSTRESS Management Committee

The EuroSTRESS programme was overseen by the Management Committee, formed by one representative of each of the participating National Funding Agencies.
(In alphabetical order)

Dr Signe Bang
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Dr Olivier Boehme
Research Foundation Flanders (FWO), Belgium

Dr Rob (R.P.W.) Heinsbroek
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Dr Sara Illman
Academy of Finland (AKA), Finland

Dr Teresa Ottinger
Swedish Research Council (VR), Sweden

Dr Mark Palmer
Medical Research Council (MRC), United Kingdom

Dr Aysim Yilmaz
Swiss National Science Foundation (SNF), Switzerland

EuroSTRESS Review Panel

The independent international Review Panel, formed of leading experts in the field, oversaw the scientific aspects of the programme. The Review Panel played a key role in the selection and review process.
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Department of Psychiatry and Neurochemistry, Sahlgrenska Academy/University of Gothenburg, Sweden

Dr Paul Grossman
Department of Psychosomatic Medicine, University Hospital Basel, Switzerland

Professor Heinz Walter Krohne
Institute of Psychology, Johannes Gutenberg University, Mainz, Germany

Professor Robert Murison
Department of Biological and Medical Psychology, University of Bergen, Norway

Dr Inez Myin-Germeys
Department of Psychiatry and Neuropsychology, Maastricht University, Belgium

EuroSTRESS Scientific Committee

The Scientific Committee of a EUROCORES Programme consists of all Project Leaders and the EUROCORES Programme Coordinator and is responsible for proposing and agreeing on the networking and dissemination activities and for reporting to the Management Committee.
(In alphabetical order)

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Leiden/Amsterdam Center of Drug Research, Leiden University, Leiden, The Netherlands

Professor Jacob Koolhaas
Department of Behavioral Physiology, University of Groningen, Haren, The Netherlands

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Institute of Behavioral Sciences, University of Helsinki, Finland

Professor Bea R.H. Van den Bergh
Tilburg School of Social and Behavioral Sciences, Tilburg University, The Netherlands

EuroSTRESS ESF Programme Coordinators

Dr Lars V. Kristiansen, 2011

Dr Nathalie Spielewoy, 2010

Dr Maria Manuela Nogueira, 2009-2010

Dr Thomas Bruhn, 2007-2009

Dr Mariana Resnicoff, 2006-2007

2.
The Collaborative Research Projects (CRPs)

The EUROCORES Programme EuroSTRESS comprised the following five collaborative research projects (CRPs), bringing together researchers from Belgium, Finland, the Netherlands, Norway, Sweden, Switzerland and the United Kingdom.

Temperament, synaptic plasticity and adaptive capacity: influence of stress during adolescence (STRESS DURING ADOLESCENCE)

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This CRP has focused on adolescence as an important developmental period modulating adult adaptive capacity in an interdisciplinary approach in humans and animals. First, we addressed the question of how stress during adolescence might modulate adult stress vulnerability. Secondly, we tested the hypothesis that individual variation in coping with stress and the mechanisms of synaptic plasticity are fundamental determining factors of adult adaptive capacity.

It is well recognised that only a small proportion of individuals develop depression after stressful life events or chronic mild stress. We tested the hypothesis that social stress during adolescence affects the adult capacity to cope with environmental stressors. Our studies in children show that social stress affects temperament traits and HPA (hypothalamo–pituitary–adrenocortical) axis reactivity during early adolescence, whereas late adolescents seem to be more resilient. In rats, social stress during adolescence does not affect adult measures of generalised anxiety, but affects specifically social learning processes, social anxiety and aggression and reduces adult impulsivity, in particular in the more impulsive, proactive males. Moreover, social stress during adolescence disrupts the normal development of adult personality structure.

Studies aimed at the underlying neurobiological mechanisms focused on the molecular processes of synaptic plasticity. Brain derived neurotrophic factor (BDNF) and activity-regulated cytoskeleton associated protein (Arc) are two key molecules in this process. Experimental blockade of Arc in the hippocampus during a critical time window disrupts learning and memory processes. Social defeat during adolescence induces a brain-region-specific increase in Arc and BDNF gene

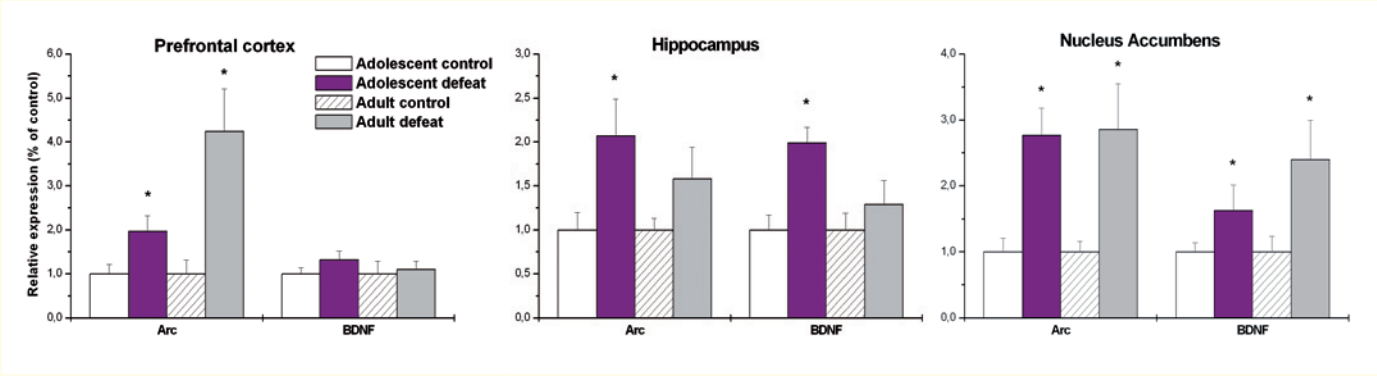

Figure 1.
The figure illustrates that adolescent social stress differs from adult social stress in the brain region specific up-regulation of key molecules of synaptic plasticity. ©Jaap Koolhaas

expression (hippocampus, prefrontal cortex and nucleus accumbens). Adult social stress induces a markedly different pattern of Arc and BDNF gene expression with significant interaction effects with temperament traits. This is consistent with the idea of adolescence as a sensitive developmental period. The presumed role of synaptic plasticity in the development of adult adaptive capacity is supported by the relationship between a functional polymorphism of the BDNF gene and the vulnerability to childhood adversities as found in the human study. Studies aimed at the causal involvement of these molecular processes in adult stress vulnerability are still in progress.

Publications directly related to the project

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Vulnerable phenotypes for stress-related mental disorders: focus on glucocorticoids (BALANCE)

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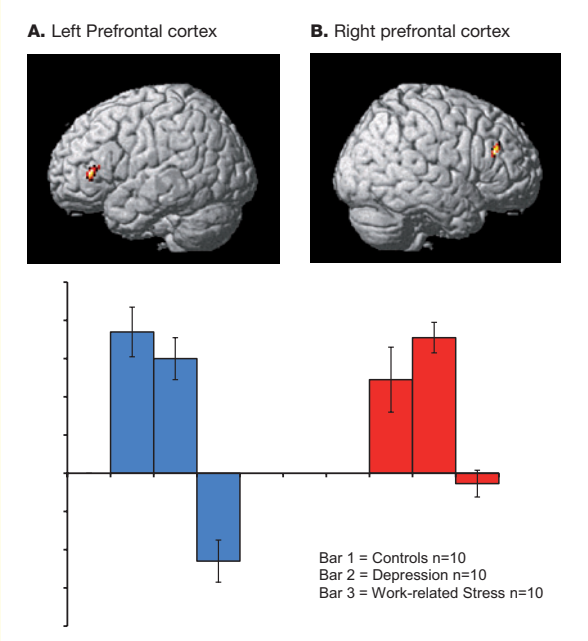

Figure 2.
Effect of MR and GR manipulations on plasma CORT levels in response to 40 minutes restraint stress, N=8-11 per genotype, values are mean±SEM. Analysis of the area under the curve reveals that low GR leads to a greater stress response, however, high MR in concert with reduced GR, can minimise the HPA axis overshoot in response to stress, suggesting that under stressful conditions MR provides a feedback signal. Thus, there is interaction between GR and MR in HPA axis feedback control after stress.

A fundamental question in stress research is why some individuals become vulnerable to mental disease while others gain resilience from stressful experiences. We focus on the hypothalamo – pituitary – adrenocortical (HPA) axis, notably adrenal cortisol/corticosterone (CORT) that targets limbic brain in control of emotional arousal, cognition and motivation. These actions exerted by CORT are mediated by mineralocorticoid and glucocorticoid receptors (MR and GR) which operate in balance to maintain homeostasis from appraisal of stressful situations to memory storage and affective responses. We test the hypothesis that imbalance in MR:GR mediated processes threatens mental health and promotes the progression of Alzheimer's disease. Briefly we can report the following highlights:

Using genetically engineered mice with differential MR and GR expression in the forebrain, the Edinburgh group found that these receptors interact in specific domains of neuroendocrine and cognitive control but for other limbic-associated behaviours each receptor mediates its own repertoire of responses. The Leiden team demonstrated that resistance of cognitive performance to the effect of prior stress exposure is observed in mice with genetic deletion of MR in the forebrain. Hence, CORT actions via limbic MR are crucial for adequate behavioural adaptation. Significant associations were identified by the Basel group of human genetic variations in stress-related genes including the genes encoding MR and GR, with emotional memory-related phenotypes.

The Umeå researchers demonstrated that exhaustion syndrome is more likely to develop in anxiety-prone, worrying, pessimistic individuals with persistent and low executive personality drive, while being characterised by a different pattern of frontal brain activation in working memory tests as compared to healthy controls and patients with depression (Figure 2). The team also found that mild-moderate Alzheimer's disease patients show significant alterations in the regulation of the HPA axis, which may aggravate and accelerate dementia. In women this is linked to increased secretion of the pro-inflammatory cytokine IL-6, while preliminary observations show associations of cognitive function with MR polymorphisms.

In conclusion, the significance of the MR:GR balance under stress was validated in transgenic animal studies; evidence for the translational significance of MR and GR was demonstrated in human genetics analysis and in studies on exhaustion syndrome and Alzheimer's disease.

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After the end of the project in spring 2012 a joint paper will be written for a high-impact journal with the achievements of this CRP.

Developmental origins of stress and mental health (DOME)

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Factors leading to stress-related disorders may be traced back to the prenatal environment. Mechanisms by which these prenatal environmental exposures operate to change biobehavioural stress mediators are not understood. Animal studies suggest that prenatal overexposure to glucocorticoids – as a consequence of exogenous exposures or experimental manipulations, which alter the function of the feto-placental glucocorticoid barrier – may be a mechanistic factor. The overall objective of this CRP has been to address these programming mechanisms and translate the evidence derived from the animal experiments into testable hypothesis in unique human cohorts.

The Amsterdam IP has contributed to the CRP's general aim of investigating how adverse early life experience and genetic background in concert evoke lasting changes in signalling pathways within the brain, resulting in altered behaviour and increased vulnerability to negative effects of stress in adulthood by investigating how prenatal stress through undernutrition affects later health and wellbeing.

The Helsinki IPs have contributed to the CRP's objectives by examining how a suboptimal prenatal environment and also exposure to traumatic events later in life may evoke changes in the stress physiological systems and induce risk of mental health. Specifically we investigated if exposure to glycyrrhizin in maternal licorice consumption during pregnancy (inhibitor of the placental glucocorticoid barrier) associates with alterations in diurnal and stress-induced HPA axis functioning, autonomic nervous system functioning, cognitive functioning

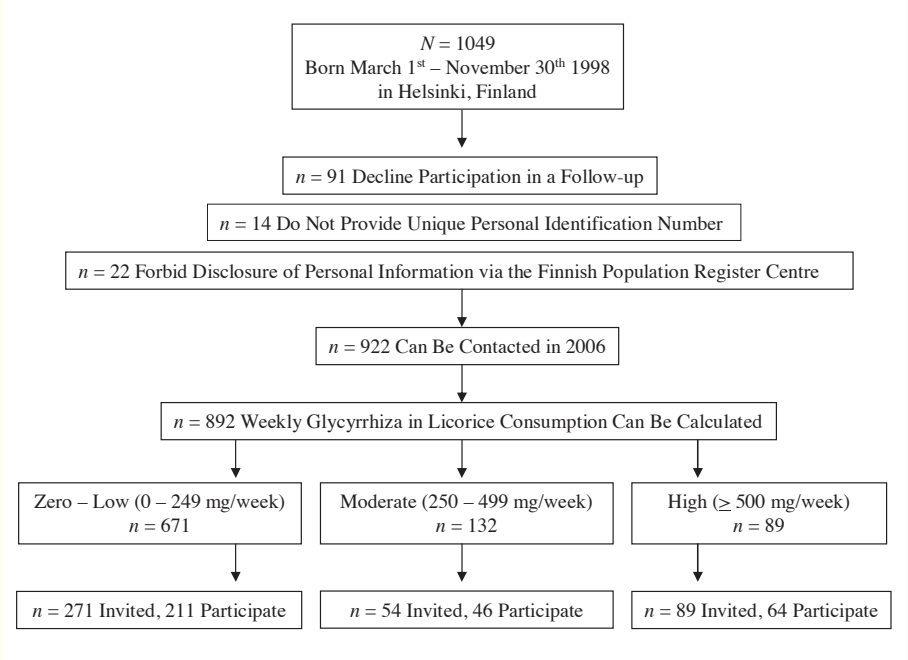

Figure 3.
Study design and selection of the participants assessed for an association between maternal licorice consumption and detrimental cognitive and psychiatric outcomes in their children at 8.1 years of age, Helsinki, Finland.

and mental health in children. The study pertaining to early traumatic events relates to separations of children from their biological parents during World War II and has tested if exposure to these early traumatic events affects later health and wellbeing.

We have shown that early environmental adversities (prenatal and in early childhood) affect later cognitive function, stress sensitivity and mental health. This CRP has thus addressed fundamental questions central to the EuroSTRESS programme providing novel mechanistic insights into how adverse early life experiences influence risk of subsequent stress-related disorders. In addition to multiple original papers we have distributed our findings via reviews. We have also actively spread this scientific knowledge to the lay public through our own websites and press releases.

Publications directly related to the project

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The effect of prenatal stress on HPA-axis function and neurodevelopment: a gene-environment interaction study (PELS)

Project Leader

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Figure 4.
Measurement of early sensory-cognitive development in the offspring: event related brain potentials and item of the Bayley Scale of Infant Development. © Bea Van den Bergh

Animal studies have shown that exposure to early life stress at moments when critical developmental processes are taking place in the central or autonomous nervous system (CNS, ANS) and/or in neuronal circuits involved in the hypothalamo–pituitary–adrenocortical (HPA) axis may induce epigenetic changes that alter later function of the stress system and cause more anxiety, enhanced stress sensitivity and impaired cognitive and emotional development, especially in genetically susceptible individuals.

Our design involved recruiting pregnant women in the UK (n = 151), Belgium (BE; n = 170) and the Netherlands (NL; n = 190), and collecting maternal stress, anxiety and depression data with self-report questionnaires and with physiological measures (cortisol, heart rate) and DNA in mother and child. In the offspring, saliva cortisol before and after inoculation in 2–4-month-olds were measured in Belgium. In the Netherlands, auditory (2–4 months) and audio-visual (9–10 months) event related brain potential (ERP) measures were taken as well as saliva cortisol and heart rate variability measures. In all countries birth outcome data were collected and the Bayley Scales of Infant Development as well as a behavioural inhibition task were administered at 9–12 months. Data collection at 9–12 months after birth is ongoing.

Preliminary results indicate that maternal mood was only weakly associated with maternal cortisol during pregnancy. However, relationships between maternal stress during an arithmetic task and parasympathetic nervous system activity as reflected in heart rate variability in first and third trimester were identified. Maternal anxiety was related to early sensory-cognitive development, i.e. the ERP-study indicates that 2- to 4-month-olds of highly versus low anxious pregnant mothers process auditory Information in a different way and at 9 months scores for receptive language are lower. So our data essentially confirm that maternal mood in pregnancy is associated with altered neurodevelopmental outcome.

In ongoing analyses we examine the importance of timing, specificity and chronicity of stressors, of gene versus environment interaction (i.e. specific candidate genes related to HPA-axis and ANS functioning) and epigenetic changes, in predicting offspring outcome. Final results of our CRP may lead to prevention and intervention strategies focusing on minimising the risks prenatal stress poses for later (mental) health.

Publications directly related to the project

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3.
Facts and Figures

Research Funding

Research funding was generated from seven European funding agencies, through the European Science Foundation (ESF). The selection of project proposals was achieved through a two-stage process, with outline proposals being sifted by the international EuroSTRESS Review Panel (which included leading academics from five European countries), and full proposals for collaborative research projects (CRPs) being selected by the Review Panel on the basis of reports submitted by international expert referees.

Eventually, out of the 11 outline proposals, four CRPs obtained funding, which included 16 individual project teams (of which three were externally funded) and two associated partners. The duration of projects was between three and four years, depending on the funding granted under national rules and regulations.

The following funding agencies supported the EUROCORES Programme EuroSTRESS:

- Research Foundation Flanders (FWO), Belgium
- Academy of Finland (AKA), Finland
- The Netherlands Organisation for Scientific Research (NWO), The Netherlands
- Research Council of Norway (NFR), Norway
- Swedish Research Council (VR), Sweden
- Swiss National Science Foundation (SNF), Switzerland
- Medical Research Council (MRC), United Kingdom

The research budget granted by national funding agencies participating in the EUROCORES Programme EuroSTRESS exceeded 3 M€.

Networking and Dissemination Funding

EuroSTRESS networking activities were collaborative activities (e.g. symposia, summer schools, etc.) that brought together scientists from at least two collaborative research projects and, on occasion, external experts in order to discuss, plan and implement future collaboration and interaction. Until the end of 2008, coordination and networking by the European Science Foundation was covered through the EC FP6 Programme, under contract number ERASCT-2003-980409. Since January 2009, national funding agencies participating in EUROCORES programmes have provided the networking budget on the principle of a common pot.

The EuroSTRESS networking funding also covered short-term visits of junior scientists to other CRP labs as well as dissemination activities that were intended to deepen the impact of the research and strengthen the field by facilitating the dissemination of results while raising the profile of the EUROCORES Programme EuroSTRESS as a whole.

Networking and Dissemination Activities

Networking and collaboration within a EUROCORES Programme take place at two levels: between the various individual projects within each collaborative research project (CRP), and between the funded CRPs within the programme as a whole. The intra-CRP collaboration is motivated by the nature of the CRP's research objectives, i.e. by the scope and the complexity of the questions it deals with. In a CRP, the participating groups have the opportunity to gather the required critical mass to successfully address the objectives and challenges of their project. The cross-CRP networking and collaboration – more on which can be found in this chapter – is stimulated by the aims and the nature of a particular EUROCORES programme. The EuroSTRESS programme has been developed precisely because of the clear need for enhanced collaboration in this field. The funded CRPs have collectively set up and further streamlined this new collaboration. To this end, the CRPs have engaged their members and, when of clear benefit, colleagues from outside the programme, in joint activities such as symposia or schools. Through the enthusiastic participation of scientists in the above-mentioned activities, not only have existing collaborations been enhanced, but also new and strategic partnership opportunities have been identified. Furthermore, these activities provided opportunities to explore aspects of the EuroSTRESS programme which are not covered by the funded research projects. The integrative activities between the CRPs have helped to strengthen the field by building coherence within this emerging research community, and served as a platform for the research work which is done in the programme. Further information can be found at the programme website www.esf.org/eurostress by clicking on 'Events'.

The following activities were organised and funded through the EuroSTRESS networking and dissemination budget:

- **EuroSTRESS launch meeting**
  23 September 2008, Brussels, Belgium
  Organised by the European Science Foundation.

The EuroSTRESS launch meeting was attended by most Project Leaders, some Principal Investigators and Management Committee members as well as the ESF staff in charge of EuroSTRESS. The structure, management and objectives of the EuroSTRESS programme were explained and possible networking and dissemination events discussed. The Project Leaders also had the opportunity to present their collaborative research projects.

- **EuroSTRESS at the PENS Summer School on 'Neurodevelopmental Programming and Phenotypic Plasticity: Implications for Stress, Aging and Health'**
  6–13 September 2009, Rhodes, Greece
  Organised by Professor Ronald de Kloet, Professor Efi Kitraki, Dr Danielle Champagne, Dr Onno Meijer.

This school aimed at training PhD students and young postdocs in concepts from gene and neural circuitry to neuroendocrine regulation and behaviour with a translational perspective. The theme of the school was neurodevelopmental programming of the stress regulating system as a modulator of health through the lifespan, with impact on longevity. The emphasis was on multidisciplinary approaches to brain research in the area of stress, neurodevelopment, cognition and behaviour with focus on the underlying brain mechanisms leading to healthy ageing and increased 'healthspan'. Each day was dedicated to a specific theme and started with a keynote lecture followed by three

Figure 5.
Group photo PENS Summer School, Rhodes, Greece, 6-13 September 2009. ©Ron de Kloet

shorter lectures. Student participants then presented key elements of the morning talks, and in the afternoon student assignments were prepared and presented before dinner. The quality of these presentations was truly outstanding, reflecting both the participants' enthusiasm and their dedication to the objectives of their study. While most of the 40 predominantly female students enrolled were from EU countries, 25% came from outside the EU, including one student from Africa. The school received very high evaluations from both students and faculty and there would be a clear demand for a repeat in the future. The financial support came equally from the EuroSTRESS programme, the EU-Lifespan consortium, the Programme of European Neuroscience Schools, and the Royal Netherlands Academy of Arts and Sciences.

- **Symposium on 'Early life events, early brain behaviour development and later cognition, emotion and health'.**
  10 May 2010, Tilburg University, Tilburg, The Netherlands
  Organised by Professor Bea Van den Bergh.

The aim of this symposium was to disseminate scientific knowledge about one of the questions the EuroSTRESS programme set out to investigate: How can early life experience and genetic background in concert evoke lasting changes in signalling pathways within the brain, resulting in altered behaviour and increased vulnerability to negative effects of stress in adulthood? The participants discussed both the influence of early adversity on brain-behaviour development as well as early influences on mental health problems and stress-related health problems. The symposium was attended by scientists and clinicians as well as some civil servants.

- **EuroSTRESS Day with Scientific Committee meeting**
  25-27 August 2010, Gravensteen, Leiden, The Netherlands
  Organised by Professor Ronald de Kloet.

This network activity was centred around the mid-term review and an outlook on the second half of the programme's running time. It was attended by all Project Leaders and many Principal Investigators and project members who first discussed the progress reported by the collaborative research projects. In a second step, their strengths and weaknesses, opportunities and threats were identified and their interactions were discussed beyond what is currently funded. The EuroSTRESS Day was followed by the 7th World Congress on Stress organised by Professor Graham Burrows and Professor Ronald de Kloet in the Gorlaeus Laboratoria in Leiden.

- **Short-term visit awarded to Odilia Laceulle,**
  PhD student of Professor Johannes Ormel, to visit Professor Vivette Glover's lab at Imperial College London
  London, UK, 5–26 February 2011

The purpose of this short-term visit was to set up a project resulting in a joint paper comparing sensitivity to stress from early childhood to adolescence while taking into account differential sensitivity (e.g. moderation of prenatal maternal anxiety). Findings suggested that being exposed to stressful events was related to higher levels of problem behaviours but not at all ages. The paper resulting from the short-term visit is currently under review: Laceulle, O'Donnell, Glover, O'Connor, Ormel, van Aken & Nederhof. Stressful events and psychological difficulties: testing alternative candidates for sensitivity. *J. Am. Acad. Child Psy.* (submitted).

- **Symposium on '(Early) life stress, brain development and ageing: The use of different methods in measuring cognition and brain function throughout life'**
  2 March 2011, Tilburg, The Netherlands
  Organised by Professor Bea R.H. Van den Bergh, Professor Katri Raïkkönen.

This symposium had two aims: First, to give an overview and discuss how human brain development/ageing and cognitive function can be measured with specific methods throughout life, from the foetal life period until old age, and secondly, to present empirical evidence of lifelong programming of human brain development/ageing and cognitive function by (early) life stress, in interaction with genetic and

epigenetic factors. The presentations were made by internationally renowned speakers who focused on methods which can be used within as well as outside the clinical context and in smaller or large cohort follow-up studies. They explained the use of different methods and presented empirical evidence of programming of human cognitive development, brain development and ageing.

- **Symposium on 'Mismatch Hypothesis of Psychiatric Disease'**
  11–13 May 2011, Groningen, The Netherlands
  Organised by Dr Esther Nederhof, Professor Johannes Ormel, Professor Ronald de Kloet.

From animal research we know that environmental cues can steer development in a direction that is adaptive to the expected later environment (adaptive phenotypic plasticity). A mismatch between expected later environment and actual circumstances decrease chances for survival and reproduction. This phenomenon has been widely studied in animals using cues from the physical environment. Since stress in Western societies is however mainly psychosocial in nature, the symposium focused on the mismatch hypothesis with regard to psychosocial stress.

- **Symposium on 'Stress and Mental Health'**
  21 June 2011, Umea, Sweden
  Organised by Professor Ronald de Kloet, Professor Tommy Olsson.

The symposium gave a multifaceted overview of stress and mental health which included epidemiological data from the Helsinki birth cohort study suggesting that early life events may predict later intellectual performance. In experimental approaches in humans and rodents newly developed techniques showed that it is possible to evaluate basic process of emotion and cognition early in life in humans and that social stress can influence temperament traits during early adolescence. In contrast, late adolescence seems to be relatively resilient for the influence of social stress on indicators of human adaptive capacity. In rodents, behavioural studies in combination with detailed electrophysiological and molecular techniques are dissecting out the underlying mechanisms behind differences in reactivity to social stress during adolescence and adulthood.

- **School on 'Conceptual Issues in Stress Research'**
  1-6 November 2011, Erice, Italy
  Organised by Professor Jacob Koolhaas, Professor Eberhard Fuchs and Professor Andrea Sgoifo.

The aim of this school was to have an in-depth discussion on conceptual issues in stress research between PhD students and experts in the field of stress research. In addition to three of the four EuroSTRESS Project Leaders, nine international experts contributed to the programme. Each speaker addressed a few major issues related to the interpretation of their results. The students discussed these issues in small groups after which they reported in a plenary session with all participants. The school covered the wide range of scientific disciplines involved in stress research. Topics included stress faced by feral animal species in nature, the molecular neurobiology of emotional learning and memory, assessing stress in human epidemiology and developmental programming in humans and animal models. The school was supported by the Ettore Majorana International School of Ethology.

4.
Final Evaluation

The purpose of the final evaluation is for a dedicated Review Panel of international experts (details of whom can be found on page 5) to assess the scientific cooperation and the interactions among the investigators, and to identify the achievements of the EuroSTRESS programme and the lessons to be learned for potential follow-up initiatives within or outside of ESF.

The assessment was based on the scientific achievements highlighted by the project leaders as well as the usefulness and impact of the networking, training and dissemination activities undertaken during this period. To this end, investigators were asked to highlight the activities that proved most useful to each CRP, providing one example to illustrate each case. The balance between input and output indicated whether the CRPs made good, optimal or insufficient use of the EuroSTRESS programme.

On the basis of the CRP reports and the call for proposals, Review Panel members were asked to provide an objective assessment of the achievements of the EuroSTRESS programme. These individual assessments then formed the bases of discussion for the Final Review Panel meeting, which was held via a teleconference. The outcome of this meeting was a consensus statement which is included below, a document which provides a collective, objective assessment of the achievements of the EuroSTRESS programme, identifying strengths and weaknesses and making recommendations for potential follow-up initiatives.

Consensus Statement for EuroSTRESS

The ESF EUROCORES scheme represents an ESF funding and networking instrument that stimulates collaboration and research integration between funded research programmes at the European level. In connecting 16 funded Principal Investigators (PIs) from seven countries in four Collaborative Research Projects (CRPs) over three years, the EUROCORES programme on stress and mental health (EuroSTRESS) truly appears to have provided an important platform to ensure connectivity and progress in a complex research field such as the understanding of stress in humans.

Collaboration and scientific output (publications)

It is the consensus opinion of the Review Panel that the EuroSTRESS programme has efficiently and successfully stimulated collaboration among leading investigators from the area of stress and mental health research. The programme, which represents a multiannual integrated effort that spans a broad spectrum of research disciplines with a translational and gene–environmental objective, has through this collaboration generated an added value that would have been difficult to reach as individually funded research projects. The exchange of ideas and expertise led to results that could not have been achieved outside the scope of this broad network.

A valid indicator of a fruitful collaboration is the number of publications that have been generated during the programme. In particular those publications involving co-authors from collaborative projects within the single CRPs as well as across CRPs should be considered as good indicators for

collaboration. In this context, the programme has resulted in an impressive number of publications in high- and top-ranking journals. These range from papers with a focus on mechanisms underlying stress such as synaptic plasticity to studies on the effects of environmental adversities on later cognition and mental health, gene–environment interactions, maternal emotions and offspring psychophysiology and endocrinology.

The DOME and PELS projects in particular should be lauded for their publications. Both of these CRPs exhibit many outstanding publications most of which involve PIs within and across the respective CRPs. This not only indicates high productivity among the involved researchers but also very importantly reflects high levels of collaboration within and across the two CRPs.

In assessing cooperation within the individual CRPs of the EuroSTRESS programme, the Review Panel has noted a certain imbalance. Whereas some have performed excellently, others appear to have had a slower start. Strictly based on the number of publications, the BALANCE CRP is assessed below average. However, other indicators show that collaboration within this CRP has been catching up and functioning well. Also, 'Stress during Adolescence' which started later so far only modestly contributed to the goal of collaboration in terms of publications. However, this CRP has been involved in organising several networking events towards the latter part of the programme.

Furthermore, the Review Panel has noted that the basis for an evaluation of the programme at this stage may be somewhat premature due to the fact that several studies are still ongoing and have to be completed over the next months. The Review Panel therefore expects to see more output, specifically integrating data and findings within and between CRPs during the next one to two years. Overall, EuroSTRESS definitely established a close collaboration among leading scientists and their research groups which would likely not have been possible without this programme.

Networking and training

A particular strength of the EuroSTRESS programme appears to have been the exchange of ideas and concepts at the various meetings. The EuroSTRESS programme has in this context resulted in high levels of activity from the start with several joint networking meetings, workshops and two schools. These activities started very early with the summer school in Rhodes in 2009 and will continue through November of 2011.

The value of training the next generation of researchers is highly visible in the programme. A large number of PhD students and postdoctoral researchers have been involved in the programme in the context of education and training. To a certain extent, exchange visits, albeit mostly within CRPs, have also enabled young researchers to share expertise and ideas. This is especially timely given the imminent retirement of several senior European stress researchers.

Overall, the programme is evaluated as highly successful in terms of networking and training. All CRPs have been actively participating in joint activities and meetings both within and across CRPs. The programme has been particularly instrumental in creating a dynamic and cohesiveness within the area of stress research at the European level. This has resulted in a strong European alliance, possibly even resulting in the creation of a European Stress Society, joint European publications and future European grant applications as discussed during a meeting between all CRPs in June this year.

Overall assessment

The potentials of all four CRPs in the EuroSTRESS EUROCORES Programme appear to have been well realised. The basic scientific structure set-up in the EuroSTRESS programme call has been followed excellently. Examples are current gene–environment interaction models as well as translational animal and human studies. The operational definitions of environmental stress versus individual stress reactions are fairly well followed. Population studies form a central part in this. By specifically studying early traumatisation and adolescent experiences, the programme has given important insights that may be applied in future clinical studies on children and adolescent populations as well as in adult psychiatric and psychological studies.

The programme has already achieved one major goal — it puts Europe in the forefront of relevant research on stress and mental health in the spirit of its initial concept. Over the coming years, this success will stand out even more.

In the opinion of the Review Panel, a programme such as EuroSTRESS would have been even more valuable had a more extensive gene-association set-up been applied. Such an approach could involve a GWAS approach, and/or the study of a wider range of pre-hoc candidate genes, as well as a renewed phenomenological analysis of what stress really is.

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