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Psychosocial Stress, Mental Health and Salivary Cortisol in Children and Adolescents

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Science is just one of the many ideologies that propel society and it should be treated as such.

Paul K Feyerabend (1975) in *How to defend society against science*

ABSTRACT

Stressful experiences and conditions in childhood influence the health and well-being of the growing individual, and can also confer a long-lasting impact into adult life. Delineating the social, mental and biological aspects of stress in children and adolescents is therefore of great concern for human beings. Despite these notions, much knowledge is lacking regarding stress in childhood.

This thesis aimed at examining diverse aspects of stress in children and adolescents: associations between social conditions, traumatic life events, mental health, and salivary cortisol as a measure of the activity of a major physiological stress system. Cross-sectional samples included two non-clinical samples of school-aged children (N=240-336) and adolescents (N =400), and two clinical samples of children with obsessive-compulsive disorder (OCD) (N =23) and adolescents who had experienced childhood abuse (N =15). Main measures were salivary cortisol sampled three times a day, and questionnaires to teachers, parents and children with questions about each child's mental health, traumatic life events and about the socioeconomic situation of the parents.

The main findings include observation of 1) higher cortisol levels in children with a moderate level of psychosocial burden (low socioeconomic status, immigrant family, social impairment of mental health problems), 2) higher cortisol levels in children with OCD who also displayed a tendency to decreasing cortisol in the face of an acute stressor, and 3) cortisol was positively related to mental health problems in abused adolescents. Furthermore, the deleterious effect of 4) traumatic events involving a social dimension, interpersonal traumas, and 5) cumulative traumatic events, polytraumatization, on the mental health of children and adolescents was indicated.

The findings are discussed with respect to the complex interactions between social, mental and biological aspects of children and adolescents. The consequences of adverse experiences in childhood may represent pathways to future health problems. Consideration of the social circumstances in childhood might in the future guide public health policies and the identification of target groups for preventive interventions as well as leading to improvements in treatment for children exposed to severe stress.

SVENSK SAMMANFATTNING

Stressfyllda erfarenheter och omständigheter under barndomen påverkar hälsan och välmåendet hos den växande individen och kan också lämna långsiktiga avtryck upp i vuxen ålder. Att klarlägga de sociala, mentala och biologiska aspekterna av stress hos barn och ungdomar är därför av stor betydelse för människan. Trots detta saknas mycket kunskap om stress i barndomen.

Syftet med denna avhandling var att undersöka mångsidiga aspekter av stress hos barn och ungdomar genom att undersöka samband mellan sociala omständigheter, traumatiska livshändelser, psykisk hälsa och salivcortisol som ett mått på aktiviteten hos ett viktigt fysiologiskt stressystem. Tvärsnittsdata inkluderade två stickprov med skolbarn (N=240-336) samt ungdomar (N=400), samt två kliniska stickprov med barn med tvångssyndrom (OCD, obsessive-compulsive disorder) (N=23) samt ungdomar utsatta för barnmisshandel (N=15). Huvudsakliga mätmetoder var salivcortisol som mättes tre gånger per dag, samt enkäter till lärare, föräldrar och barn om barnens psykiska hälsa och traumatiska livshändelser, samt om familjens socioekonomiska situation.

Betydelsefulla fynd inkluderar: 1) högre cortisolnivåer hos skolbarn med en måttlig grad av psykosocial belastning (låg socioekonomisk status, immigrantfamilj, sociala svårigheter p.g.a. psykiska problem), 2) högre cortisolnivåer hos barn med OCD som också uppvisade en tendens till sjunkande cortisolnivåer som reaktion på en akut stressor, och 3) cortisol korrelerade positivt med psykisk ohälsa hos traumatiserade ungdomar. Därutöver påvisades indikationer av betydelsen av 4) traumatiska händelser med en social dimension, interpersonella trauman, och 5) kumulativa traumatiska livshändelser, polytraumatisering, för den psykiska hälsan hos barn och ungdomar.

Fynden diskuteras med hänvisning till de komplexa interaktionerna mellan sociala, mentala och biologiska omständigheter samt dess följder för barn och ungdomar. Erfarenheter i barndomen kan utgöra risk för hälsoproblem senare i livet, och kunskap om mekanismerna mellan sociala omständigheter och ohälsa kan på sikt vägleda utformningen av folkhälsostrategier och preventiva insatser. Dessutom skulle denna kunkap kunna leda fram till förbättrad behandling för barn och ungdomar utsatta för svår stress.

LIST OF PAPERS

This thesis is based on the original publications, which are referred to in the text by their Roman numerals I - V.

- I. Gustafsson, P.E., Gustafsson, P.A., Nelson, N. Cortisol levels and psychosocial factors in preadolescent children. *Stress and Health*, 2006; 22: 3-9.
- II. Gustafsson, P.E., Gustafsson, P.A., Ivarsson, T., Nelson, N. Diurnal cortisol levels and cortisol response in youths with obsessive-compulsive disorder. *Neuropsychobiology*, 2008; 57:14-21.
- III. Gustafsson, P.E., Nelson, N., Gustafsson, P.A. Diurnal cortisol levels, psychiatric symptoms and sense of coherence in abused adolescents. *Nordic Journal of Psychiatry (accepted for publication, 20080416)*.
- IV. Gustafsson, P.E., Larsson, I., Gustafsson, P.A., Nelson, N. Traumatic life events, sociocultural factors and psychiatric symptoms in preadolescent children. (*submitted*).
- V. Gustafsson, P.E., Nilsson, D., Svedin, C.G. Polytraumatization and psychological symptoms in children and adolescents. *European Child & Adolescent Psychiatry (accepted for publication, 20080908)*.

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ABBREVIATIONS

11β-HSD 11β-hydroxysteroid dehydrogenase

ACAdrenal cortex

ACTH Adrenocorticotropic hormone

Adrenal medulla AMANOVA Analysis of variance

ANS Autonomic nervous system

AUC Area under the curve

CA Child abuse

CAR Cortisol awakening response

CBG Corticosteroid-binding globuline

CD Conduct disorder

C-GAS Children's Global Assessment Scale

CGI Clinical global impression

CP Conduct problems CPA Child physical abuse

CRH Corticotropin releasing hormone

CSA Child sexual abuse **CSF** Cerebrospinal fluid Ctrl Healthy control group CV Coefficient of variation

Children's Yale-Brown Obsessive Compulsive Scale CY-BOCS

DNA Deoxyribonucleic acid

DSM Diagnostic and statistical manual of mental disorders

DST Dexamethasone suppression test

EIA Enzyme immunoassay ES **Emotional symptoms** EXT Externalizing symptoms **FSC**

Family social class

GAD Generalized anxiety disorder

GC Glucocorticoid

GR Glucocorticoid receptor (type 2)

HDL High-density lipoprotein HPA Hypothalamic-pituitary-adrenal

HT Hypothalamus IF Immigrant family

IFN Interferon
IL Interleukin

INT Internalizing symptoms

IP/IPE Interpersonal/interpersonal events

IQ Intelligence quotient

K-SADS-PL Schedule for Affective Disorders and Scizophrenia for

School-Age Children – Present and Lifetime version

LDL Low-density lipoprotein

LITE Life Incidence of Traumatic Events checklist

MD Major depresion

MR Mineralocorticoid receptor (type 1)

M-W Mann-Whitney U test

nIP/nIPE Non-interpersonal/non-interpersonal events

nmol/L Nanomol per liter NR Not reported

OCD Obsessive-compulsive disorder

PT Polytraumatization

PTS, PTSS Posttraumatic stress symptoms PTSD Posttraumatic stress syndrome

PVN Paraventricular nucleus of the hypothalamus

SAM Sympathetic-adrenomedullary

SDQ Strengths and Difficulties Questionnaire

SES Socioeconomic status
SOC Sense of coherence

SSRI Selective serotonin reuptake inhibitors

TMB Tetramethylbenzidine
TNF Tumor necrosis factor

TSCC Trauma symptom checklist for children

UFC Urinary free cortisol

PROLOGUE

The health of children is important for several reasons. First and foremost, according to the Convention on the Rights of the Child, children have the right "to the enjoyment of the highest attainable standard of health" (United Nations, 1991). The convention emphasizes the well-being of the child as a goal in itself. Furthermore, today there is substantial evidence for the importance of experiences of the growing individual in affecting health and well-being later in life. This notion highlights the significance of circumstances experienced in early life, for the health of the adult. Thus, children's health is of significance across the whole life span.

The importance of the social environment for human beings cannot be stressed enough. Starting at the beginning of life with the attachment between child and caregiver, it continues throughout child- and adulthood with increasingly complex layered relationships, giving us opportunity to thrive. This social nature of humans has served us well throughout evolution, as Peter Kropotkin described in Mutual Aid over a century ago (Kropotkin, 1902). On the other hand, when social conditions are unfavorable, we can become mentally and physically ill. Whether this social adversity takes the form of a broader social hierarchy, or as traumatic interpersonal experiences, it has an impact on our biopsychosocial self, disturbing us as a whole in the same way as when our life is in danger. The key factor may be the loss of trust in others, which we take for granted. This impact of social conditions is one representation of what might be called stress. Children can be especially susceptible to stress, being attentive to the social milieu they are born into, and which they are dependent on. Stress in childhood impacts not only on the child momentarily, but may also have significance for their entire life. Affecting mental and biological elements of the child, stress has consequences for the physical and mental health and well-being, making them vulnerable in the life they just entered. Similarly, the biological elements of the child influence the mental and social functioning of children, highlighting the complexity of interactions during development.

Knowledge about particularly harmful experiences in childhood can be useful for the immediate surroundings of children, e.g., the family and healthcare, and can aid the selection of preventive efforts. This also includes building a society that makes supportive contexts achievable for all children. Knowledge about the variety of biological, mental and social consequences of stress in the growing individual may guide us in supporting the children to whom society have failed granting healthy settings for development, including improvements of treatment approaches in healthcare. Studying the impact of stress in childhood may therefore yield powerful tools for improving health and well-being of both children and adults. A small piece adding to this important research field will be presented in this thesis. Enjoy.

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INTRODUCTION TO STRESS

A Brief History of Stress

Stress, as a concept in modern science, is usually described as having its roots in the middle of the 19th century when Claude Bernard (1813-1878) introduced the term "milieu intérieur" to denote the dynamic internal environment necessary for living organisms (Chrousos & Gold, 1992; Goldstein & Kopin, 2007; Le Moal, 2007). In the beginning of the 20th century, Walter Cannon (1871-1945), in his studies on the sympathetic-adrenal system, coined the term "homeostasis" for the maintenance of physiological variables, as well as the principle of negative feedback for its regulation. Cannon introduced the "fight or flight reaction" as the catecholamine response to a wide variety of harmful stimuli, and demonstrated the role of catecholamines in the control of homeostasis. In the 1930s Hans Selye (1907-1982) studied the pituitary-adrenocortical system and popularized the concept of "stress", a term he transferred from mechanics to physiology. He defined stress as the non-specific response of the body to any demand placed upon it.

Although Selve met opposition in his own disciplinary field of laboratory physiology, his stress theory was received with interest by other societal groups, such as those within psychosomatics, practicing physicians, and importantly within the military medicine, industry, and in the popular domain (Viner, 1999). All these actors found the stress theory appealing, as it offered a convenient framework in line with the purpose and desires of each group. Through acceptance in these other domains, the stress concept eventually found its way back into the academy, where it spread into a great variety of disciplines and subdisciplines. The stress research field thereafter developed in a number of different general traditions, as described by Vingerhoets & Marcelissen (Vingerhoets & Marcelissen, 1988). To begin with, the biologically oriented research tradition can be viewed as a continuation of the work of Cannon and Selve, focusing on the physiological responses to various stimuli. The classic psychosomatic approach, based on the notion of specific intrapsychic conflicts as the cause of somatic disease, later developed into two directions; personality factors and specific psychological states as predisposing to disease. The life event approach (Paykel, 2001) originating in the social sciences, focusing on distinct environmental experiences as causes of disease, received attention as a result of the work of Holmes & Rahe and their Social Readjustment Scale (Holmes & Rahe, 1967). The transactional approach is a main psychological tradition where the focus lies on the subjective aspects of stress, such as the appraisal of and coping with threats (Lazarus & Folkman, 1984). The life style focused on behavioral approach has reactions to stress and work/organizational stress approach (Frankenhaeuser, 1981) has focused on the

health effects of the physical and social work conditions. The field within sociology concerned with group differences in vulnerability have examined the influence of inequality, social class, race/ethnicity, gender and marital status on vulnerability to (primarily mental) illness (Aneshensel, 1992; Kessler & Neighbors, 1986). A macrosocial tradition has investigated cultural differences in vulnerability to disease, and one faction has focused on intervention and prevention of stress at the individual, micro or macro environmental level.

During the past twenty years, research has developed further, encompassing more specialized areas, but also including integrative approaches to stress. As an example that has lead to the expansion of the biological tradition, neuroscience has become an increasingly important field in mapping the neural pathways mediating stress processing and understanding the neurobiological impact of stress, and progress has been made in integrating these findings with the social sciences. Perhaps owing to methodological advancements in physiological assessment, field research in psychobiology has evolved and research has been integrated with various other disciplines. In addition, developments in genetics have made it possible to examine specific gene-environment interactions.

It is worth noting that Vingerhoets & Marcelissen in their review do not mention any tradition with a specific interest in stress in children. Research on children has lagged behind research on adults, and it continues to do so. This is a pity since there is compelling evidence that early life stress is an important determinant of health later in life (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Dong et al., 2004; Felitti et al., 1998; Phillips et al., 1998). Expanded research on pediatric stress may therefore yield valuable knowledge for both children and adults.

Concepts of Stress

Selye's unfortunate definition of stress as the response, rather than the force, has caused much confusion since he first formulated it. As Selye (1976) later described it, his choice of word was the result of his shortcomings in the English language at the time:

It was not until several years later that the *British Medical Journal* called my attention to this fact, by the somewhat sarcastic remark that according to Selye "stress is its own cause". Actually I should have called my phenomenon the "strain reaction" and that which causes it "stress", which would parallel the use of these terms in physics. However, by the time that this came to my attention, "biological stress" in my sense of the word was so generally accepted in various languages that I could not have redefined it. (p. 50)

As a consequence, he introduced the word "stressor" for the force causing stress.

A confusing issue in the conceptualization of human stress is where in the stress process of stimulus, internal processing, and response stress fits in. As an anonymous researcher expressed it in an often-cited, humorous but apt, comment: "Stress, in addition to being itself, and the result of itself, is also the cause of itself." (Wallis, 1983). What most stress concepts have in common is the environmental conditions or changes that exceed the adaptive resources and threaten the psychological or biological capacities of the individual (S. Cohen, Kessler, & Gordon, 1997).

The stress field can be divided into three conceptual traditions based on the theoretical and methodological perspectives on stress: the biological, the psychological and the environmental traditions (S. Cohen, Gordon, & Kessler, 1997). Although these traditions surely are connected and implicit or explicit definitions of stress often are mixtures from these three traditions, a description of them may serve a heuristic purpose in disentangling the focus on the environment, the psychological processing and the physiological response.

The biological tradition, as noted above, follows the tradition of Cannon and Selye in focusing on the physiological response to stressors, and the definition of stressors as causes of the physiological response. This definition makes objective operationalizations of stress possible. Later definitions of stress include "a state of disharmony, or threatened homeostasis" (Chrousos & Gold, 1992), or "a condition where expectations [...] do not match the current or anticipated perceptions of the internal or external environment" (Goldstein & McEwen, 2002), and focuses on the role of physiological mediators in reestablishing the homeostasis, as in the allostatic model (McEwen & Seeman, 1999). The physiological stress response will be considered in more detail later on.

The psychological tradition, on the other hand, places emphasis on the organism's interpretative perception and evaluation of the threat, and thus represents a subjective conceptualization of stress. Stress is viewed as the particular type of relationship between a person and the environment, which taxes or exceeds the person's resources (Lazarus, 1990). According to this cognitive-relational model of stress (Lazarus & Folkman, 1984), appraisal is the cognitive evaluation of a transaction between a person and its environment, with regard to the degree to which the situation is perceived as threatening (primary appraisal), and the availability of resources (secondary appraisal). If the situation is perceived as stressful, the individual activates a coping process to mitigate the situation. Coping refers to the cognitive and behavioral efforts to deal with demands that are appraised as taxing or exceeding the person's resources. Coping can aim at regulating stressful emotions (emotion-focused coping) or at altering the person-environment relation to relieve the distressing situation (problem-focused coping).

In the social sciences, the focus has been on the environmental component of the stress process, the stressors, and stress conceptualizations have aimed at defining the nature of stressors. The biomedical definition of stress as the physiological response state of the body, and of stressors as the causes of stress, is of little use in the social sciences, since it defines the environmental component with reference to something that is traditionally not measured by social scientists (Wheaton, 1996). Stress in the social sciences was for a time synonymous with its dominant operationalization as life events. Later, the physical term "strain" was transferred to the social sciences in the context of chronic distress (Pearlin, 1989; Pearlin & Johnson, 1977). A more recent definition of stressors by Wheaton is "conditions of threat, demands, or structural constraints that, by the very fact of their occurrence or existence, call into question the operating integrity of the organism." (Wheaton, 1996). This emphasizes the group perspective to stress: the stressor is untangled from the individual appraisal, coping and physiological response. Stressors can be defined by their place on a continuum of the duration of the stressors. Life events are discrete, objective changes (e.g., divorce of parents or starting school), while chronic stressors on the other end of the continuum are enduring problems, conflicts and threats, often without a clear onset or termination (e.g., difficulties at school or at home) (Pearlin, 1989). Other examples are daily hassles, macro stressors, nonevents, and traumatic events (which will be considered in more detail below). An additional focus of the environmental approach is the structural context of stressors, mediators, responses and outcomes (Aneshensel, 1992) and the arrangement of social institutions and roles and role sets (Pearlin, 1989). Recently some authors have argued for an environmental perspective in the study of stress and psychopathology in children and adolescent (Grant, Compas et al., 2003).

Although stress research has focused primarily on the negative aspects of stress, Selye made the distinction between distress and eustress, the former representing unpleasant or harmful stress and the latter pleasant or healthy stress (Selye, 1976). This distinction is also evident in the division of the appraisal into (threat of) harm and challenge, the latter denoting the positive aspects of stress (Lazarus & Folkman, 1984). This thesis concentrates on stress as a potentially harmful part of human life and stress will be used in this sense, if not otherwise noted. Nevertheless, it should be noted that challenges are also a prerequisite for positive development and growth; biologically, psychologically and socially.

A Metamodel of Stress

Stress research obviously is a wide field encompassing many traditional disciplines, with adaptations of the stress concept to fit it into each discipline. For example, concepts of stress relying on the physiological response are of little use in the social sciences (Wheaton, 1996) - it is adapted to a biomedical paradigm, with the human body as the system under study. Similarly, a model of stress including environmental demands as a prerequisite (S. Cohen, Kessler et al., 1997) does not fit in with biomedical stress research of within-body stressors (e.g., hypoglycemia or pain). This has created many different concepts of stress, which can be seen as a problem due to the inconsistent use of the term (McEwen, 2008).

The stress concept has most often been used with a focus on the individual. However, stress is sometimes applied at higher levels, such as stress resulting from demands on the community brought about by natural disasters, terrorist attacks or disease pandemics (Landau, 2007; Shamai, Kimhi, & Enosh, 2007), or on the family by death, financial shortages and community violence (Bowlby-West, 1983; Conger et al., 2002; M. Lynch & Cicchetti, 2002). In the biomedical field stress-related concepts are also used with different meanings than in the classical sense. The allostatic load model (McEwen, 1998) for example, concerns the physiological "wear and tear" caused by stress hormones, corresponding to "chronic stress" but with reference to physiological - not interpersonal - interaction. Stress is also applied at a cellular level in the context of oxidative stress (Finkel & Holbrook, 2000), referring to the accumulation of reactive oxygen species, which is a potential threat to the cellular homeostasis. Amusingly enough, the notion that psychosocial stress contributes to oxidative stress (Epel et al., 2004) takes us back to the question where to fit in "stress" in the stress process, albeit at another level.

The reason why the stress approach is so adaptable to widely different fields, with superficially little in common, may ultimately rely on an implicit system theoretical perspective in the stress approach. Thus, a potentially functional adoption of the term, which could be useful for describing insults and demands on open systems in general, might be achievable. A general formulation of stressors could be "threats to the homeostasis or to the achievement of the goals of a specific system", and the stress response as "the active response of a specific system to a homeostatic or goal-impeding threat". According to this formulation, stress is not conceptualized with an exclusive focus on the individual, but as demands or challenges on any open system, which may be social, psychological or biological. These stress processes in different systems influence each other reciprocally through their interfaces (Sluzki, 2007). The structure of any system may influence responses and resilience to stress. As such, the genetic make-up, as a structural template (Kandel, 1998), may influence the physiological stress response (DeRijk et al., 2006; Uhart, McCaul,

Oswald, Choi, & Wand, 2004) and the psychological adjustment to severe stress (Binder et al., 2004; Jaffee et al., 2005). Factors such as organizational structure and communication in social systems may also influence the impact of systemic stress (Walsh, 1996, 2007). The structure may also be influenced, e.g., through environmentally induced long-term transcriptional changes (Lee, Brady, & Koenig, 2003) or through family therapy (Minuchin, 1974). See Table 1 for examples of similar stress-related concepts at different systemic levels. The benefits of a systemic approach to stress has been noted previously (Steinberg & Ritzmann, 1990), but this perspective has not, apparently, been explicitly integrated into stress research.

Several points argue for a more explicit systemic approach in stress theory. First, as described, stress is conveniently applied at several other system levels than those typically conceptualized. This may be an expression of either heuristically useful analogies or of more substantial system isomorphisms (von Bertalanffy, 1968), and thus may represent functional adaptations of the term. Here, a general stress concept tying together the different domains may be helpful in integrating research efforts.

Moreover, there is overwhelming evidence for reciprocal influences in stress physiology beyond the feedback function. Despite this, the stress process is most often described as a top-down linear phenomenon. Reciprocality is also evident in social systems, and in interaction between individual and social systems through the behavioral interface. Furthermore, the multitude of complex interactions at different hierarchical levels, which comprise any stress process, is best understood when focusing on the whole instead of specific parts. This move away from reductionistic approaches is also present in the study of biological systems (Neugebauer, Willy, & Sauerland, 2001; Van Regenmortel, 2004). A disturbance of one system is always at risk for spreading to subsystems or to adjacent systems and further. Any single pathway is ultimately a simplistic description of the complex whole that constitutes the reality for the human being. A systems perspective may be especially appropriate when studying children, who are very much dependent on the function of the immediate social systems (Bronfenbrenner, 1979; Minuchin, 1974), and who are under constant development (Gottlieb, 1998).

Table 1. Examples of equivalent aspects of stress across systemic levels of human organization, and examples of interface content. Note that a stressor at a given level may also produce stress at both a higher and a lower level, as can adaptations.

Aspects of stress and interface content

System level

Chronic stressors Tr	Traumatic stressors	Adaptations	Resilience
		•	
Inequality	• War	Political changes	Cohesion
Poverty	 Natural disaster 		 Equality
	 Epidemics 		
nterface: wor	-Interface: working and neighborhood conditions, action -	d conditions, action -	
Economic	 Death of family 	 Rearrangement 	 High warmth
shortage	member	of roles	 Distinct
Violence in		 Marital discord 	boundaries
neighborhood		 Harsh parenting 	
Interface: be	- Interface: behavior, experiences, social relationships -	ocial relationships -	
	1	1	
Bullying	 Child abuse 	 Internalization 	• Sense of
Isolation	 Severe accident 	Aggression	coherence
Discrimination		• Long-term	 Polymorphisms
		potentiation	
- Interface:	- Interface: biological stress systems, interoception -	ns, interoception -	
Allostatic load	 Physical trauma 	 Disease 	 Genetic make-up
	 Intoxication 	 Healing 	 Previous
		 Epigenetic changes 	experience

General Models of Association

Here two unifying approaches will be summarized, both present in different stress research traditions and relevant for the present thesis.

Specificity and Non-Specificity

The specificity approach concerns the uniqueness of relations between stressors (the putative cause) and the outcomes of the stressors (McMahon, Grant, Compas, Thurm, & Ey, 2003; Monroe & Johnson, 1990). This approach can be divided into four hypotheses. Full or pure stressor-outcome specificity is present when specific stressors cause specific outcomes, that is; the relationships are unique for both causes and outcomes. Stressor specificity or multifinality is a specific stressor causing a number of outcomes. Conversely, outcome specificity or equifinality is a number of stressors causing the same outcome. Non-specificity is present when a number of stressors all cause a number of outcomes. See Figure 1 for a sketch of these hypotheses.

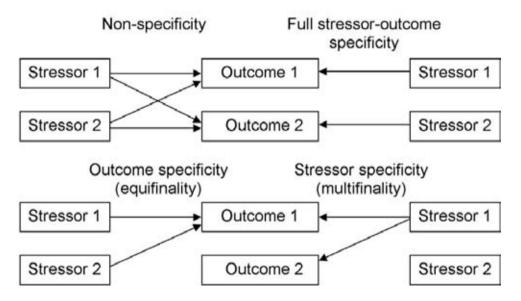


Figure 1. A display of principal hypotheses concerning specificity of stressors and responses/outcomes, for the basic condition of two stressors and two outcomes.

Although both the stressors and outcomes measured in stress research vary greatly, this principal approach is present in both biological and psychosocial stress research.

The study of the physiological stress response has continuously been regarded with respect to specificity. Selye strongly emphasized its non-specificity (Selye & Fortier, 1950), or to use another term, equifinality (similarity in outcome). Later a degree of specificity (dichotomous response) was introduced (H. Y. Li & Sawchenko, 1998; Mason, 1971; Munck, Guyre, & Holbrook, 1984), and recently more complex stressor-outcome specificity has been highlighted (Herman et al., 2003; Pacak & Palkovits, 2001). Characteristic of biomedically oriented stress research, the focus has most often been on different acute stress paradigms and physiological (and, more recently, neurocircuitry) responses in animal models. Typical examples are the effects of cold, immobilization, hemorrhage, insulin-induced hypoglycemia, formalin-induced pain and tissue damage, on the different components of the stress system (Pacak & Palkovits, 2001; Pacak et al., 1995).

Similarly, specificity perspectives have been an issue in more psychosocially oriented stress research (Garber & Hollon, 1991; McMahon et al., 2003; Monroe & Johnson, 1990). Here, the principal focus has been on psychosocial stressors, and mental health or psychopathology outcomes in humans. As in biomedical stress research, the initial model was one of non-specificity, as in the change being the essential component of life events in affecting general health (Holmes & Rahe, 1967). As the outcome under study shifted to an increasing degree from biological towards psychological constructs, the idea of non-specificity came into question in favor of stressor-specific models based on the predictability, controllability, and desirability of stressors (Burke, 1996). Examples of specificity issues are the effect of separation versus conflict life events' on depressive versus conduct symptomatology (Sandler, Reynolds, Kliewer, & Ramirez, 1992), the diverse psychopathological consequences of parental separation (Fergusson, Horwood, & Lynskey, 1994), or the differences between social etiology and social causality models (Aneshensel, 2005). The question about specificity is also present in more integrative stress research, such as in examining which categories of acute psychological stressors that are able to elicit a cortisol response (Dickerson & Kemeny, 2004), or different patterns of cortisol secretion in children exposed to different types of maltreatment (Cicchetti & Rogosch, 2001a).

A specificity line of thought can be discerned in all papers of this thesis. Outcome specificity in cortisol secretion at different times of the day is, at least implicitly, considered, with respect to: psychosocial stressors (Paper I), OCD diagnosis (Paper II) and trauma-related symptoms (Paper III). Different dimensions of mental ill health are also considered in relation to different types of stressors (socioeconomic, and interpersonal and non-interpersonal traumatic events) in Paper IV and V.

Cumulative Burden

The cumulative model assumes that it is the accumulation of a variety of factors across different domains, rather than single factors by themselves, that confer the main impact of stressors, and that there is an additive (linear) or multiplicative (threshold) dose-response relationship. Thus, the cumulative model is a model of stressor non-specificity. Although not always formulated in a stress framework the cumulative model is of excellent use in stress research. The original formulation of "cumulative risk" has an epidemiological heritage, but in explicit stress studies, the term "cumulative stressors" are sometimes used (Morales & Guerra, 2006; Stewart, 2006). Other perspectives that share the focus on cumulativity of social disadvantage are the ecological (Bronfenbrenner, 1979) and life course (Elder, 1998) theories of human development. The cumulative model is usually applied as a convenient summation index of dichotomized risk factors.

The notion that the accumulation of risk factors over time is related to child development has its origins in the epidemiological research on social risk related to mental health and cognitive development in children, and was first presented in the results of the Isle of Wight Study (Rutter, Tizard, Yule, Graham, & Whitmore, 1976), and later in the Rochester Longitudinal Study (Sameroff, Seifer, Zax, & Barocas, 1987). This "social disadvantage tradition" has, ever since, continued to study the influence of social factors at different levels, on the mental health of children (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Atzaba-Poria, Pike, & Deater-Deckard, 2004; Deater-Deckard, Dodge, Bates, & Pettit, 1998; Morales & Guerra, 2006) and later in life (Chapman et al., 2004). More recently the cumulative model has been applied in the epidemiology of children's somatic health (Bauman, Silver, & Stein, 2006; Forehand, Biggar, & Kotchick, 1998; Larson, Russ, Crall, & Halfon, 2008), and measures of allostatic load (Evans & Kim, 2007).

Trauma research is another field concerned with child development where the cumulative model has been brought to attention. Influenced by the work of Rutter, Finkelhor and co-workers have pioneered its introduction to the field and have given it a new name, polyvictimization (Finkelhor, Ormrod, & Turner, 2007a). This will be described in more detail below.

From a pathophysiological position a variant of the cumulative model has also been given consideration in the form of the allostatic load model, described in more detail later on. In short, the allostatic load model refers to the physiological changes in stress mediators that an organism must undertake to adapt to challenges (allostasis), and the cumulative burden for the body these changes confer (allostatic load), with potential pathological consequences (McEwen, 1998). The allostatic model differs somewhat from the other cumulative traditions since it is not stressors proper that are considered in the cumulative

risk, but physiological mediators of stress. Nonetheless, in the way it is formulated and operationalized, these mediators are viewed as proximal causes to pathological states, exerting a cumulative "wear and tear" on the body, and thus the principal models are analogous. The cumulative allostatic model has been used in the study of health and mortality outcomes related to aging (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997) and as related to socioeconomic status (SES) in children (E. Goodman, McEwen, Huang, Dolan, & Adler, 2005).

Within the different traditions there has also been a move towards considering the risk factors from a multilevel perspective of social (Atzaba-Poria et al., 2004; Bronfenbrenner, 1979) or biological (McEwen & Seeman, 1999) structure, emphasizing the hierarchy of systems.

The arguments for the cumulative model are largely similar in all three traditions. First, adverse factors have a tendency to cluster, and, as a result, the consideration of the factors singly gives a simplified, reductionistic picture. In the social disadvantage perspective, this concerns the multifaceted "environment of poverty" (Evans, 2004) that unprivileged children endure: bad housing, family turmoil, community violence, etc. In the trauma perspective, it is expressed as the clustering of trauma and the increased risk for revictimization (Finkelhor, Ormrod, & Turner, 2007c), be it due to psychosocial risk or some other factor. In the allostatic model, it is attributed to the functional interactions between physiological systems (Seeman, McEwen, Rowe, & Singer, 2001).

Second, the added effect of several factors makes a contribution to the outcome to a degree that may not be discernible when the factors are considered by themselves. As examples of this, in the Isle of Wight Study a non-linear effect was found signifying that the risk factors potentiated each other. In the trauma research field, an effect of a cumulative victimization index eclipsing the impact of single events has been indicated (Finkelhor et al., 2007a). Similar conclusions have been made from an allostatic load perspective, explained by the joint contribution of multiple physiological systems to disease (Seeman et al., 2004).

Third, there is the idea of non-specificity that states that it is the total burden by itself rather than the sum of specific combinations that is causally or otherwise related to the outcome.

A cumulative approach is applied in several papers in this dissertation. In Paper I, a cumulative index of psychosocial load is examined in relationship to diurnal cortisol secretion. In Paper IV and V, the cumulative impact of trauma on the mental health of children and adolescents is considered.

IMPACT OF PSYCHOSOCIAL STRESS IN CHILDHOOD

In the present thesis two categories of psychosocial stressors, socioeconomic disadvantage and traumatic events, are of special interest and will therefore receive some extra attention in the following sections.

Socioeconomic Disadvantage and Social Stressors

Socioeconomic Disadvantage and Health

The hierarchical arrangement of our society comes at a great cost. The relationship between social disadvantage and ill health is well established (Adler & Ostrove, 1999). Since parents are an important link between the social structure and the child, the impact of social conditions on adults is also of interest for this discussion. A number of factors such as occupational status, financial resources and income and educational level – often collectively referred to as socioeconomic status (SES) – and ethnical minority status, neighborhood disadvantage and single parent household (in reality, most often mother-headed) both co-occur and interact in their effects on the child (Luthar, 1999), with diverse and pervasive consequences for children's well-being.

Socioeconomically disadvantaged children have been shown to be at risk for low birth weight, neonatal mortality, birth defects or other birth complications, growth stunting, lead poisoning, iron deficiency, injury (and subsequent death caused by injury), respiratory illness, sensory impairment, complications of infections and longer periods spent in bed and in hospital (Bradley & Corwyn, 2002; Brooks-Gunn & Duncan, 1997). They are also at increased risk for developmental delay, learning disability, academic course failure, school grade retention, placement in special education, dropping out of school and worse performance on achievement and IQ tests, compared to higher-SES peers (McLoyd, 1998). Low-SES or poor children also have worse mental health, such as externalizing and internalizing symptoms, conduct disorder, depression, delinquency and drug abuse (Costello et al., 1996; Costello, Farmer, Angold, Burns, & Erkanli, 1997; Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005; Luthar, 1999; McLeod & Shanahan, 1993; McLoyd, 1990, 1998). Although children with immigrant background often are assumed to have worse mental health, the literature is inconclusive, perhaps owing to methodological issues (A. Goodman, Patel, & Leon, 2008; Stevens & Vollebergh, 2008).

Most studies on the topic of social disadvantage and child mental health have been done in other countries than Sweden. However, Swedish health inequalitites seem to be largely comparable, with increased health risks among disadvantaged children across a wide range of physical and mental health problems (Bremberg, 2002).

Different views regarding the association between socioeconomic condition and health have been emphasized during the years (Adler & Ostrove, 1999). During the early "poverty era" (before 1985) a threshold model was dominant, where ill health was viewed as a function of material shortages below a certain poverty level, with negligible variation explained by SES above that threshold. In the mid-1980s, this model was challenged by the social gradient model. This model appeared due to mounting evidence that risk factors, morbidity and mortality for a wide array of diseases increased over the whole SES spectrum, from the highest to the lowest (Adler et al., 1994; Marmot, 1999; Marmot, Shipley, & Rose, 1984). Since the general acceptance of this model, models further explaining the SES-health link have been the main focus. Stress-based models are particularly appealing since they make it possible to link the social, psychological and biological systems in a single framework.

Social Influences on Health from a Stress Perspective

The social patterning of mental health has been a field of study since the 1930s. Since then, two competing models about the causal direction of the SES-health relationship have been debated (R. J. Turner, Wheaton, & Lloyd, 1995). The social selection model posits that mental ill health produce downward social mobility and selection. However, the social causation model, attributing the association to exposure variations between social strata, is today given more evidential weight for most disorders (Adler & Ostrove, 1999; Aneshensel, 1992). This model is compatible with classical stress theory.

Social stratification, by social class, ethnicity and gender, can influence stress exposure of adults and children by different mediators, e.g. by increased exposure to life events (Brady & Matthews, 2002; Grant, Finkelstein, & Lyons, 2003; Pearlin, 1989). A number of chronic stressors also mediate the relaionship, e.g., economic hardship, discrimination, segregation and residing in violent neighborhoods (Attar, Guerra, & Tolan, 1994; Belle & Doucet, 2003; Garcia Coll et al., 1996; Golding, Potts, & Aneshensel, 1991; Grant, Finkelstein et al., 2003; Pearlin, 1989). These mediators are strongly interrelated, e.g., involuntary job loss may confer economic hardship for a family and marital conflict may lead to divorce, which in turn may increase the economic burden and strain in parental roles, especially for women who tend to be left with the main responsibility for the child (Belle, 1990; Pearlin & Johnson, 1977).

The family system and the parents are important links by which the social structure, indirectly, can exert its influence on children (Conger et al., 2002; Grant, Compas et al., 2003; McLoyd, 1990). Economic hardship (due to unstable work conditions, low family income, debts and income loss) permeate

the daily lives of the family, by not being able to meet material needs, falling behind in paying debts, and the need to cut back on everyday expenses (Conger et al., 1992, 1993). Less developed social networks and perceived social support make low-SES parents even more vulnerable to turmoil (Evans, 2004). For immigrated parents, additional burden may entail prejudice, discrimination and segregation (Garcia Coll et al., 1996), in addition to the stress involved in the migration process (Stevens & Vollebergh, 2008). This constant hardship can influence the mood of the parents and cause them to become more depressed, demoralized, pessimistic and emotionally unstable (Conger, McCarty, Yang, Lahey, & Kropp, 1984). These mood changes may in turn lead to marital conflict and affect parenting practices, towards less nurturing, supportive and involved, and more hostile, coercive and harsher, with inconsistent discipline, which directly affects the socioemotional development of the child (Conger et al., 1993; Conger, Ge, Elder, Lorenz, & Simons, 1994). These linkages between the social system, family system and the individual child may also affect biological systems, e.g., through activation of physiological stress systems.

Furthermore, the psychosocial impact of hierarchy and inequality by itself has been emphasized as an important cause of ill health (Belle & Doucet, 2003; Sapolsky, 2005; Wilkinson, 1999), displayed in the international association between income inequality and poor adult and child physical and mental health and mortality (Pickett, James, & Wilkinson, 2006; Pickett & Wilkinson, 2007; Wilkinson & Pickett, 2006, 2008). This association might be explained by lower social cohesion, greater insecurity, mistrust, and the pervasive feeling of inferiority (Charlesworth, Gilfillan, & Wilkinson, 2004; Sapolsky, 2005; Wilkinson, 1999). Thus, socioeconomic disadvantage could be considered a chronic stressor itself, in addition to being a risk factor for increased stressor exposure or vulnerability.

Traumatic Stressors in Childhood

$Consequences\ of\ Childhood\ Trauma$

Today much is known about the potential consequences of traumatic experiences in childhood, and there is extensive evidence that failure to resolve moderate to severe traumatic reactions result in both short term and long-term adverse consequences. Examples of traumatic experiences for children are sexual abuse (Briere & Elliott, 1994; Kendall-Tackett, Williams, & Finkelhor, 1993), physical abuse and violence (Osofsky, 1995; Runyon, Deblinger, Ryan, & Thakkar-Kolar, 2004), disaster (Green et al., 1991), terrorism (Fremont, 2004), and accidental injury (Mirza, Bhadrinath, Goodyer, & Gilmour, 1998; Stoddard & Saxe, 2001). There is no single "trauma syndrome", but children exposed to trauma are at risk of developing a wide range of diagnoses and/or symptoms affecting overall functioning of the child (J. A. Cohen, Berliner, &

Mannarino, 2000; Fremont, 2004; Kendall-Tackett et al., 1993; Osofsky, 1999). The most common psychiatric disorders following trauma in children is acute stress disorder as well as posttraumatic stress disorder (PTSD) (Fremont, 2004; Osofsky, 1999). In PTSD the child may re-experience the trauma by flashbacks or nightmares, and in younger children, themes from the trauma may appear in repetitive play or reenactment of traumarelated material. Avoidance of traumassociated situations, numbing and withdrawal from the external world may occur, as well as increased arousal.

The long-term consequences for the child are diverse, with increased risk for a variety of mental health and psychopathology problems besides PTSD, e.g. depression, suicidality, eating disorder, sexual disorders, decreased self-esteem, interpersonal problems, substance abuse, delinquent behavior and medical problems (Chapman et al., 2004; Molnar, Buka, & Kessler, 2001; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Saunders, 2003; Silverman, Reinherz, & Giaconia, 1996; Widom, 1999).

Children's reactions are related to the characteristics of the trauma (e.g., type, level of exposure, duration), developmental factors and available resources, both internal (e.g., influenced by interpersonal skills, previous trauma exposure) and external (e.g., support from the parents) (Fremont, 2004; Osofsky, 1999). The immediate social environment plays a vital role in helping the child to moderate experiences, and the presence of a parent with whom the child has a stable, secure, emotional relationship, is of great importance for successful coping (Power, 2004; Proctor et al., 2007). However, the parents' ability to support the child may directly or indirectly be compromised by the child's traumatization (Fremont, 2004; Osofsky, 1999). Social support at the community level is also an important determinant in supporting the pathways to successful coping with trauma (Walsh, 2007).

Definition of Traumatic Stressors

Traumatic stressors belong to a special class of stressors, and they are often conceptualized as a subclass of life events. The definition and the specific properties of traumatic stressors have caused much controversy, including difficulties in drawing the principal distinction between traumatic events and other life events (Kasl, 1990).

The most commonly employed definition has been the one included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1980, 1987, 1994), where a traumatic event is defined as a part of the diagnosis of posttraumatic stress disorder (PTSD), included as a diagnosis since 1980. The DSM-IV (American Psychiatric Association, 1994) specifies the exposure "experienced, witnessed or confronted with", to a traumatic event "that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others" (Criterion A1). DSM-IV

continues with specifying that the person's immediate subjective reaction to the event "involved intense fear, helplessness, or horror" (Criterion A2), and both subcriteria are needed for fulfilling the stressor criterion (Criterion A) for PTSD (American Psychiatric Association, 1994). Although these attempts have been made to clarify the definition, the subject is still debated (Avina & O'Donohue, 2002; Elhai, Kashdan, & Frueh, 2005; Maier, 2007; McNally, 2003; Olff & Gersons, 2005; Weathers & Keane, 2007).

Several authors emphasize the conceptual gain in disentangling the objective event, from the appraisal and perception of, and the response to, the event (Grant, Compas et al., 2003; Green, 1990; Kasl, 1990). Common terms such as "serious threat" or "trauma" may make the distinction between the event and the appraisal of the event less clear. Similarly, there is a problem with the term "stressful event" as the event is thus predefined by its outcome. "Trauma" is also a somewhat confusing term since it is synonymous with "psychological trauma" in psychological/psychiatric (and popular) usage, while in somatic medical jargon (e.g., surgery) the same term is used to denote bodily injury.

A traumatic event is by the DSM-IV defined on an individual basis since it includes the individual's subjective response. The objective environmental component of a traumatic stressor, the occurrence of the event, thus cannot be defined as traumatic by itself but rather as a "potentially traumatic stressor" (Norris, 1992; Weathers & Keane, 2007). This term, however, merely pushes the problem to another area; almost all events are *potentially* traumatic, in the strict sense. Perhaps the problem stems from the difficulty in defining an exact boundary for a continuous dimension (stressor severity or magnitude), and the clinical need for taking the clients subjective responses into consideration. Ironically, the problem of defining a traumatic stressor as distinct from other non-traumatic stressors mimics a problem of defining a stressor per se (Kasl, 1990); a stressor is defined by the response to it, and a stressor must have a certain intensity to elicit a response.

Another problem with the DSM-IV definition is that it is specifically designed for the PTSD diagnosis. Since people, and especially children and adolescents, may react to severe life events in a number of different ways besides PTSD, this variety should, ideally, be taken into account. This is mentioned in the DSM-IV where the stressor must be of extreme, life-threatening, severity for PTSD, while in adjustment disorder a high stressor severity is not a prerequisite. The single reliance on a specific diagnosis, as the basis for defining severe experiences, may not necessarily be optimal for research purposes. Such narrow descriptions may be needed in clinical situations, while in research these constraints should not hinder empirical study. Perhaps it is sufficient to be aware of the fact that "(potentially) traumatic" stressors belong to the higher end of a hypothetical stressor severity scale, and that any distinction between low- and high-intensity stressors ultimately is arbitrary.

Dimensions of Traumatic Stressors

Although the objective occurrence of an event is the basis for the conceptualization of traumatic stressors, there are some characteristics that may aid the conceptualtization, if not in a strict definitional sense, in a descriptive sense.

Some commonly mentioned characteristics of traumatic events as distinct from common life events are "out of the ordinary", "unexpected" and "containing elements of life threat" (J. A. Cohen et al., 2000). The DSM-IV (American Psychiatric Association, 1994) exemplifies this as experience of military combat, violent personal assault, natural or manmade disasters, severe car accidents or being diagnosed with a life-threatening illness, or for children developmentally inappropriate sexual experiences with or without actual threat of violence or injury.

Green (1990; 1993) has applied a more structured approach to the description of traumatic stressors, and has defined eight dimensions at the individual appraisal level: 1) threat to one's life or body integrity, 2) severe physical harm or injury, 3) receipt of intentional injury/harm, 4) exposure to the grotesque, 5) violent/sudden loss of a loved one, 6) witnessing or learning of violence to a loved one, 7) learning of exposure to a noxious agent, and 8) causing death or severe harm to another. Of these, 3) receipt of intentional injury/harm, is of special interest for this thesis. Green describes this dimension as a subclass of 2) severe physical harm or injury. Several studies have found higher rates of PTSD and symptoms in groups exposed to interpersonal (IP, e.g., rape, physical assault) compared to non-interpersonal (nIP, e.g., vehicle accident, illness, natural death of a family member) events (Breslau et al., 1998; Green et al., 2000; Krupnick et al., 2004; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993; Shalev & Freedman, 2005). The same effect has been noted in disaster research, where people are considerably more severaly affected by actions of mass violence, than by natural or technological disaster (Norris, Friedman, Watson et al., 2002). This is also mentioned in DSM-IV, "The disorder may be especially severe or long lasting when the stressor is of human design (e.g., torture, rape)" (American Psychiatric Association, 1994). The perception of life threat is also more predictive of PTSD in IP than nIP traumas (Ozer, Best, Lipsey, & Weiss, 2003). This interpersonal or intentional dimension of trauma has not been systematically studied in children, but like for adults, the incidence of PTSD is considerable greater after interpersonal than non-interpersonal trauma (Charuvastra & Cloitre, 2008), indicating a relevance of the interpersonal dimension for children as well.

Cumulative Trauma

The majority of studies on trauma have focused on the impact of specific experiences, such as sexual abuse, combat and physical assault. However, during the last decade the effect of cumulative childhood traumas, i.e., the accumulation of different traumatic events, has been given increased attention (Finkelhor et al., 2007a; R. J. Turner & Lloyd, 1995). The focus is thus distinct from a focus on repetitive or chronic traumatic stressors (Terr, 1991), where the impact of repeated incidents or ongoing traumatic stressors, of a single type, are considered. As Finkelhor (2008; Finkelhor et al., 2007a) summarizes as "the pitfalls of fragmentation", the focus on single trauma types have several shortcomings. Fragmentation creates an isolated understanding of interrelated phenomena. This is a problem especially since there is evidence that some traumas tend to cluster (Baldry, 2003; Saunders, 2003) and that trauma may increase the risk for subsequent trauma exposure (Finkelhor et al., 2007c). Moreover, risk factors co-occur and create vulnerability for many types of traumas, and child outcomes may be largely similar for different events (Finkelhor, 2008). All these interrelationships between aspects of traumas are thus overlooked, limiting our understanding of the ecology of trauma and of children's own perspective. There is also evidence that the cumulative effect of different childhood traumas is of great importance for the subsequent development of psychiatric problems, both in children and adolescent (Finkelhor, Ormrod, & Turner, 2007b; Green et al., 2000; H. A. Turner, Finkelhor, & Ormrod, 2006), as well as later in life (Breslau, Chilcoat, Kessler, & Davis, 1999; Briere, Kaltman, & Green, 2008; R. J. Turner & Lloyd, 1995). Failure to account for cumulative trauma exposure thus leads to an overestimation of the effect of single traumas, as well as an underestimation of the total impact of trauma. A fragmentated approach also fails to identify the traumatized individuals in greatest need of intervention. In addition, the division into separate fields focusing on separate trauma types leads to duplication of efforts, unnecessary competition and reduces policy influences (Finkelhor, 2008).

Finkelhor (2007a) termed the multiple victimization of children "polyvictimization". In a similar fashion, the wider term "polytraumatization" is introduced in Paper V to indicate the exposure to multiple different traumatic events, irrespective of their juridical status or nature of the trauma.

Obsessive-Compulsive Disorder and Stress

Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by distressing and repeated intrusive thoughts, obsessions, and repetitive or ritualistic actions, compulsions, which serve to decrease the anxiety (Stein, 2002). OCD is a chronic disorder often with serious impairment (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) and is one of the worldwide leading causes of disability (Lopez & Murray, 1998). The lifetime prevalence has been estimated to 1.6% (Kessler, Berglund et al., 2005). Onset in childhood and adolescence was previously viewed as rare, but is now thought to be as common as adult onset, with child prevalence estimates between 0.25 and 3%, equal among boys and girls (Heyman et al., 2001; Rapoport et al., 2000; Valleni-Basile et al., 1994). OCD in childhood is thought to be an underdiagnosed and undertreated disorder, despite rather effective treatment options with cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRI) (Heyman et al., 2001; O'Kearney, Anstey, & von Sanden, 2006; Watson & Rees, 2008). It is a largely heterogeneous disorder and symptomatology differs somewhat from adult OCD, with development-dependent traits and patterns (Geller et al., 1998; Ivarsson & Valderhaug, 2006; C. M. Turner, 2006).

There are several indirect indications that stress and stress physiology may play a role in obsessive-compulsive disorder (Kluge et al., 2006). First, there are some connections between stress exposure and OCD. Childhood OCD is, like many disorders, more common in children of low SES (Heyman et al., 2001), and children with OCD experience more daily stress than children without OCD (Findley et al., 2003; Lin et al., 2007).

Second, there are some results of an effect of life stress, on the onset of childhood OCD (Gothelf, Aharonovsky, Horesh, Carty, & Apter, 2004), and on symptom severity for OCD in both children (Lin et al., 2007) and adults (Cromer, Schmidt, & Murphy, 2006), pointing towards a possible causal link between stress exposure and OCD severity.

Third, there is some evidence for a defective serotonin system – HPA axis link in at least adults with OCD (Khanna, John, & Reddy, 2001; Monteleone, Catapano, Tortorella, Di Martino, & Maj, 1995). OCD patients, similar to MD patients, seem to display a blunted response to administration of various serotonin agonists (Khanna et al., 2001; Lucey, O'Keane, Butcher, Clare, & Dinan, 1992; Meltzer, Bastani, Jayathilake, & Maes, 1997; Sallee, Koran, Pallanti, Carson, & Sethuraman, 1998), which has been shown to be predictive of treatment outcomes in some patients (Mathew et al., 2001). However, this blunted response may be corrected by SSRI treatment in OCD as well as in MD patients (Meltzer et al., 1997). It may also be somewhat specific to serotonin challenge, since normal cortisol responses have been found to pharmacological challenges with naloxone (an opiate antagonist) (Michelson et al., 1996),

clonidine (an adrenoreceptor antagonist) (Brambilla et al., 1997) and apomorphine (a dopamine agonist) (Brambilla, Perna, Bussi, & Bellodi, 2000).

Furthermore, several regions involved in central stress regulation, e.g., medial prefrontal cortex, amygdala and hippocampus, may be pathophysiologically important in OCD (Atmaca et al., 2008; Friedlander & Desrocher, 2006; Hong et al., 2007; Szeszko et al., 2004; Szeszko et al., 1999). Volume abnormalities in these regions have also been found in patients with major depression (MD) (Konarski et al., 2008), a commonly comorbid disorder in OCD where both the serotonin system and central stress circuits are relevant (McAllister-Williams, Ferrier, & Young, 1998; Porter, Gallagher, Watson, & Young, 2004). In adults with depression consistent HPA dysregulations have also been found (Gillespie & Nemeroff, 2005), which are thought to play a pathophysiological role in the disorder (Barden, 2004; McEwen, 2004). Although most studies have been done on adults, the prevalence of childhood-onset OCD makes it important to examine the stress-OCD link in younger samples.

Allostasis and Allostatic Load

The emotional impact of psychosocial stress in children resonates in biological systems. The human physiological stress system can be viewed as an important interface, connecting mental and neurobiological processes with other bodily systems. The model of allostasis and allostatic load has become popular to explain the biological impact of psychosocial stress. The term allostasis was originally coined by Sterling & Eyer (1988) and was later adopted by McEwen (McEwen & Stellar, 1993), who since then has developed and campaigned the model in a series of reviews (e.g., McEwen, 1998, 2007; McEwen & Wingfield, 2003). Allostasis means achieving stability through change, representing the ability of the body to maintain homeostasis by adapting physiological parameters (McEwen, 1998). The primary mediators of allostasis are those involved in the stress response, e.g., cortisol and catecholamines, which have widespread effects on bodily systems. The myriad of mediators also regulate the activity of each other, meaning that a change in one mediator leads to complementary changes in the others, resulting in a nonlinear net effect (McEwen, 2007). This is a good example of the mutual interdependence of physiological systems. On the one hand, the physiological response to environmental demands, stressors, is initially adaptive and necessary for survival. Chronic activation of the stress system, on the other hand, e.g., due to chronic or repeated exposure to stress, lack of habituation, inadequate response or failure to shut down the response when the danger has passed, results in excessive (or inadequate) exposure to stress mediators. The cumulative effect of the altered physiological state in multiple systems leads, in the long run, to "wear and tear", with potentially disease-related consequences (McEwen, 1998, 2007). This is called allostatic load or overload. As examples of expressions of allostatic load, the initially adaptive metabolic effects of cortisol are thought to lead to insulin resistance and central obesity, in people subjected to chronic stress (Kyrou, Chrousos, & Tsigos, 2006). Chronic stress also leads to atrophy of neurons in the prefrontal cortex and hippocampus, and to hypertrophy in amygdala. These brain regions also express glucocorticoid receptors, and results points towards cortisol playing a role in these effects of chronic stress (McEwen, 2007). The intricate HPA axis effects on brain structures are also implicated as a pathophysiological link between stress exposure and subsequent development of psychiatric disorders (De Bellis, 2002; McEwen, 2004; Penza, Heim, & Nemeroff, 2003). This is also an example of circular systems interactions in stress; psychosocial stress impacts on mental well-being, which can potentially lead to chronically dysregulated stress mediators. These mediators, in turn, affect neurobiological and mental systems.

Allostatic load is usually operationalized as a number of separate components, such as primary mediators (e.g., cortisol, epinephrine, norepinephrine) and secondary mediators (HDL and LDL cholesterol, glycosylated Hb, waist-hip ratio, blood pressure, cardiovascular reactivity), usually summarized in a cumulative index. This operationalization of allostatic load has been shown to be valuable in the prediction of ill health (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Karlamangla, Singer, & Seeman, 2006). Measures of allostatic load have been shown to be related to both SES and to aspects of the proximal environment (e.g., disadvantageous neighborhood, family turmoil) in children and adolescents (Chen & Paterson, 2006; Evans & English, 2002; Evans & Kim, 2007; E. Goodman et al., 2005; Worthman & Panter-Brick, 2008). Since the HPA axis is an important mediator of the stress response and of allostasis/allostatic load, and is central to this thesis, an overview of its structure and function now follows.

THE PHYSIOLOGICAL STRESS RESPONSE AND THE HPA AXIS

Upon exposure to a stressor, the human stress system is activated and elicits a stress response (Charmandari, Tsigos, & Chrousos, 2005). The stress response comprises adaptive redirection of behavior (e.g., through increased arousal and alertness and suppression of appetite) as well as physiological adaption by redirection of energy (e.g., increased blood pressure and gluconeogenesis).

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine circuit that, together with the sympathetic-adrenomedullary (SAM) system, comprises the main physiological stress response. The activity of SAM is influenced by central components in the pons (locus coeruleus) and medulla oblongata (rostral ventrolateral medulla) (Guyenet, 2000, 2006), among others. Locus coeruleus activation also leads to increased arousal through its diffuse projections in the brain (Chrousos & Gold, 1992). The SAM affects the periphery through sympathetic/parasympathetic nerves and through the release of catecholamines from the adrenal medulla, which leads to rapid effects aimed at preparing the organism for managing the threat (e.g. increased blood pressure, heart rate, cardiac output, redirection of blood flow from the splanchnic circulation to the brain and skeletal and cardiac muscles, increased respiratory rate), termed the "fight or flight" reaction. Aside from these two systems, other hormones released during the stress response are renin-angiotensin, prolactin and oxytocin (Van de Kar & Blair, 1999). A brief review of the physiology of the HPA axis is presented below. It should be noted that most studies have been done on animal models, where other glucocorticoids than cortisol may be mainly secreted, e.g., corticosterone in rodents. These will be referred to collectively as glucocorticoids, GCs.

Central Coordination of the HPA Axis

The medial paraventricular nucleus (PVN) of the hypothalamus receives a multitude of inputs relevant for eliciting the HPA response. Two principal afferent pathways to the PVN have been identified to be capable of eliciting the stress response, depending on the nature of the threat (Herman & Cullinan, 1997). Stressors directly threatening the homeostasis (e.g., a drop in blood pressure) activate autonomic receptors (e.g., baroreceptors), and information reaches the PVN through ascending neuronal pathways mainly relayed in the brainstem. This visceral pathway, carrying simple monosensoric information, elicits reflexive corticotropin-releasing hormone (CRH) release. The response is not dependent on cortical involvement and is called a "reactive response"

(Herman et al., 2003). More complex threats (e.g., a social challenge) require integration of polysensoric information and of previous experience, and therefore involve higher limbic levels, eliciting an "anticipatory response". The hippocampus is a limbic brain region involved in the storage and retrieval of declarative memory (Eichenbaum, Otto, & Cohen, 1992), and also exerts inhibitory influences on the HPA axis (Herman & Cullinan, 1997). The limbic pathways through hippocampus, as well as amygdala and prefrontal cortex, are relayed through intermediate structures (e.g., peri-paraventricular zone and other regions of hypothalamus, nucleus of the solitary tract). These intermediate structures may also mediate reactive responses, and the net stress response is therefore determined by the context-dependent summation of all relevant stimuli. The reactive response is viewed as the genetically programmed default, but it is modulated by input from higher limbic regions, and vice versa; a limbic inhibition of the stress response may by overridden by strong threats to the homeostasis. The PVN input from limbic pathways, in turn, may depend on the preferred region mediating the input (e.g., hippocampus, amygdala or the prefrontal cortex), and each stressor is today thought to display a unique neurochemical "signature" (McDougall, Widdop, & Lawrence, 2005; Pacak & Palkovits, 2001; Van de Kar & Blair, 1999). Thus, central stress circuitry is viewed as specific, integrated and hierarchical. See Figure 2 for a heuristic description of the physiological stress response.

The short- and long-term response and adaptation to stress are dependent on the developmental stage of the child (Heim & Nemeroff, 2001; Perry & Pollard, 1998). Early social influences can result in a long-lasting programming of the stress system, as has been shown in rats. Maternal licking and grooming inhibit the methylation, an epigenetic form of inactivation, of hippocampal glucocorticoid receptor (GR) genes, which persists into adulthood and influences the regulation of the HPA axis (Weaver et al., 2005). Disruption of this relationship between infant and caregiver influence brain development substantially. Forced separation or maltreatment also leads to structural brain modeling marked by HPA axis dysregulations and vulnerability to stress exposure later in life (Cirulli, Berry, & Alleva, 2003; Sanchez, 2006). Children may be especially vulnerable to adversities due to increased neural plasticity (Gunnar & Quevedo, 2007).

Later childhood and adolescence is also a period of notable structural and functional plasticity of brain regions involved in the stress response; regions that also are sensitive to the actions of GCs (i.e., the hippocampus, prefrontal cortex and amygdala) (Romeo & McEwen, 2006). Younger rats have been shown to respond differently than their adult counterparts, owing to a more substantial neuronal activation in the PVN of younger subjects during both acute and chronic stress (Romeo et al., 2006). Furthermore, the prepubertal brain has been shown to be more sensitive for acute GC effects than the adult brain (Lee et al., 2003) and there is an indication that hippocampal damage and related memory

deficits due to chronic stress during adolescence is less reversible than in adults (Isgor, Kabbaj, Akil, & Watson, 2004). However, one study indicating a more optimistic result has shown HPA dysregulations induced by early stress exposure to be reversible by an enrichment of the environment during adolescence (Morley-Fletcher, Rea, Maccari, & Laviola, 2003).

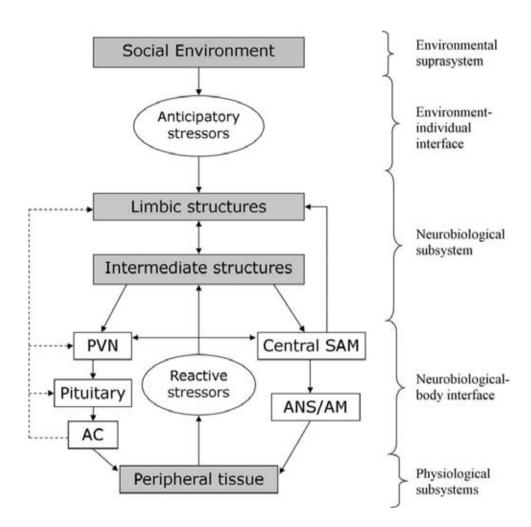


Figure 2. A simplified description of the main structures involved in the physiological stress response. See text for details. PVN= paraventricular nucleus of the hypothalamus, AC= adrenal cortex, SAM = sympathetic adrenomedullary system, ANS = autonomic nervous system, AM = adrenal medulla.

Regulation and Dynamics of Cortisol Secretion

The activation of the HPA axis is initiated by CRH secretion from the PVN. CRH reaches the pituitary through the pituitary portal circulation and induces secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary, culminating in cortisol secretion from the zona fasciculata of the adrenal cortex. GCs act on the hippocampus to regulate the basal HPA tone (proactive feedback), and at the hippocampal, hypothalamic and pituitary levels to regulate stress-induced levels (reactive feedback) (E. R. de Kloet, Vreugdenhil, Oitzl, & Joels, 1998). Upon the onset of a stressor, CRH is secreted within seconds with a 5-10 seconds delay of ACTH secretion. Cortisol concentrations start to rise within minutes and peaks at about 30 minutes after onset (Carrasco & Van de Kar, 2003; Dickerson & Kemeny, 2004).

Newborns are able to react physiologically to acute stressors, although this response can be very variable (Gunnar, 1992; Mörelius, 2006). In young children, the quality of care and the child's attachment to an attachment object are important in regulating the cortisol response to acute stress (Gunnar & Donzella, 2002). At around one year of age a period of HPA axis hyposensitivity to acute stressors supposedly appears, perhaps due to decreased adrenal sensitivity to ACTH (Gunnar & Quevedo, 2007). This hyporesponsive period is thought to continue during a large part of childhood, but exactly when it ends is not clear (Gunnar & Quevedo, 2007).

In addition to the response to acute stressors, under resting conditions the HPA axis follows a circadian rhythm with a morning peak of cortisol as a response to awakening, with lower activity during the day and night until the early morning when HPA activity slowly increases before the awakening peak (Wilhelm, Born, Kudielka, Schlotz, & Wust, 2007), "the cortisol awakening response" (CAR) (Pruessner et al., 1997; Wust et al., 2000). CAR seems to be empirically rather independent from the underlying circadian rhythm, at least during the day (Edwards, Clow, Evans, & Hucklebridge, 2001; Schmidt-Reinwald et al., 1999; Wilhelm et al., 2007), and thus, similarly to the acute response to stressors, is superimposed on the basal cortisol rhythm. In addition, CAR has been indicated to be independent from the cortisol response to psychological and pharmacological stressors (Edwards et al., 2001).

In the newborn, the typical circadian rhythm of the HPA axis is not present (Klug et al., 2000). This mature pattern of basal activity usually develops somewhere between 6 weeks and 3 months, with considerable interindividual variability (Kiess et al., 1995; Price, Close, & Fielding, 1983; Santiago, Jorge, & Moreira, 1996). This early development of a circadian rhythm is influenced by the establishment of regular sleeping patterns of the child (Gunnar & Donzella, 2002; Gunnar & Quevedo, 2007). During early childhood, the social network extends from the family to include peers and other adults, e.g. in daycare. The daily cortisol regulation is at this point influenced by the challenges this

environment presents. The perceived social competence of the child and his/her acceptance by peers may influence the HPA activity, and the support of adults may function as a buffer. Although results regarding the cortisol secretion in relation to age or puberty in childhood are contradictory (Knutsson et al., 1997; Rosmalen et al., 2005), there are some indication of changes in girls around puberty, leading to higher morning cortisol levels compared to boys (Netherton, Goodyer, Tamplin, & Herbert, 2004).

Cortisol Actions

In the bloodstream, cortisol is to a large degree bound to plasma proteins, mainly corticosteroid binding globulin (CBG), and only the unbound, free fraction (5-10%) is available to target tissues. The CBG levels are a first line post-adrenal regulator of cortisol availability. CBG synthesis is induced by estrogens and inhibited by GCs and stress (E. R. de Kloet et al., 1998). CBG is also a substrate for neutrophile elastase, which may be a way to increase GC levels locally at sites of inflammation and wound healing (Hammond, 1995). Another peripheral regulator of cortisol effects is 11β -hydroxysteroid dehydrogenase (11β -HSD), which exists in two isoforms, catalyzing the conversion of biologically active cortisol to inactive cortisone and vice versa (Tomlinson et al., 2004; White, Mune, & Agarwal, 1997). Local activity of 11β -HSD is important for modulation of local cortisol concentrations (Tomlinson et al., 2004; White et al., 1997).

Glucocorticoids exert their effects through two types of intracellular receptors: the mineralocorticoid receptor (MR, or type 1), which is aldosterone's principal receptor but also binds glucocorticoids with high affinity, and the glucocorticoid receptor (GR, or type 2), which has lower GC affinity (E. R. de Kloet et al., 1998). The different affinities of cortisol for the two receptors have an important physiological function, such as different cortisol effects depending on high or low cortisol concentrations (Joels, 2006). Ligand-bound GC receptors bind to specific DNA sites (positive or negative glucocorticoid responsive elements, GREs (Dostert & Heinzel, 2004)) and thereby stimulate or suppress transcriptional activity (Beato & Sanchez-Pacheco, 1996). GC receptors may inhibit transcription factors through protein-protein cross-talk or competition for nuclear coactivators, a process called transrepression (De Bosscher, Vanden Berghe, & Haegeman, 2003; Stahn, Lowenberg, Hommes, & Buttgereit, 2007). GCs also display some rapid effects within seconds to minutes, acting through non-genomic mechanisms via direct interaction with cellular membranes, cytosolic receptors with extranuclear effects, or membranebound glucocorticoid receptor variants (Losel et al., 2003; Stahn et al., 2007).

The general functional effects of GCs were initially described as mediating the stress response as well as having a permissive effect (Selye, 1955). Later, the GC actions during stress were conceptualized as suppressive of the

physiological response and having a restorative function in protecting the body from stress mediators (Munck et al., 1984). More recently, a synthesis of stimulating, permissive, suppressive as well as preparative (modulation of repeated responses) actions has been described (Sapolsky, Romero, & Munck, 2000).

Since GC receptors are ubiquitously distributed in the body, cortisol has the capacity to affect many organ systems. Among these effects, cortisol affects the metabolism in mainly catabolic ways to mobilize energy (Kyrou et al., 2006). Although GCs have well-known immunosuppressive effects, more recently their stimulatory and modulatory actions on the immune system have also been appreciated (Ashwell, Lu, & Vacchio, 2000; Sorrells & Sapolsky, 2007; Wilckens & De Rijk, 1997), yielding a complex picture of immonological effects of GCs. The brain is also affected, both through excitatory modulation and structural remodeling. The hippocampus is the most studied brain region in regard to cortisol, although cortisol effects also have been made evident on amygdala and the prefrontal cortex (McEwen, 2007). The hippocampus is also one of the few brain regions capable of structural plasticity in adults, and neurogenesis and reversible remodeling of the dendrites of neurons have been shown to occur in different parts of hippocampus (McEwen, 2007). This plasticity, and long-term synaptic changes (M. A. Lynch, 2004), are under the influence of cortisol actions. Cortisol may have basal and acute positive effects on plasticity, but chronic elevations are damaging, owing to the differential effects of MRs and GRs (Joels, 2001).

Physiological Systems Interactions

Although the HPA axis can be considered a distinct system, it interacts closely with other physiological systems in a bidirectional manner, over the course of development. Although a lengthy discussion of these interactions is beyond the scope of this text, a few examples will be given. To start with, at the central level of the SAM system CRH projections from the amygdala (which also stimulates the HPA axis) stimulate (Koob, 1999) while GCs inhibit SAM output (Fukuhara et al., 1996; Kvetnansky et al., 1995) and ACTH release is stimulated by catecholamines (Axelrod & Reisine, 1984). Conversely, noradrenergic efferents from the locus coeruleus stimulate the CRH release from the PVN (Koob, 1999; Pacak & Palkovits, 2001), and the CRH/NE systems work in concert to stimulate each other (Chrousos & Gold, 1992). In the periphery, GCs regulate the biosynthesis of catecholamines (Axelrod & Reisine, 1984; Pohorecky & Wurtman, 1971), as well as enhancing the cardiovascular effects of adrenaline and noradrenaline (Sapolsky et al., 2000).

Aside from the actions of GCs on the immune system, many cytokines (e.g., IL-1, IL-6, TNF- α) also stimulate the HPA axis together with the catecholamine secretion (and inhibits the reproductive axis and the thyroid axis), while a few

cytokines (IL-4 and IFN- γ) may inhibit HPA activity (Turnbull & Rivier, 1999). The principal effects are evident during the threat of infection, but results also indicate that the HPA axis is immunologically activated in other forms of stress, such as psychological, as well as during basal HPA activity. Cytokines are thought to act mainly through central HPA axis stimulation along several possible pathways, e.g., local prostaglandin production and stimulation of the vagus nerve in peripheral tissue (Turnbull & Rivier, 1999).

The HPA axis also interacts with the reproductive system (Chrousos, 1998). Centrally, CRH and GCs inhibit gonadotropin-releasing hormone secretion from the arcuate and preoptic nuclei. GCs also suppress luteinizing hormone secretion at the pituitary level, sex steroid secretion of the gonads, and increase the peripheral resistance of their effects. During inflammation, cytokines exerts inhibitory influences on the reproductive axis both directly through cytokines, and indirectly through cytokine activation of the HPA axis. Again, the interaction is bidirectional; estrogens stimulate the CRH expression centrally and the CBG synthesis peripherally (Kajantie & Phillips, 2006).

PSYCHOSOCIAL STRESS AND THE HPA AXIS

HPA Axis Dysregulations

The psychobiology of the HPA axis is a huge research field, and it is beyond the scope of this discussion to give a comprehensive review of the literature. Only a few basic assumptions guiding this thesis will be mentioned below, based on the more fully developed literature on adults, and then the findings in populations relevant for this thesis will be reviewed.

Deviation may be in Either Direction

The classical view of stress-related HPA changes was that severe stress would lead to increased long-term activity, as observed in depressed patients (Gillespie & Nemeroff, 2005). This idea was challenged after the HPA axis in PTSD was given attention, soon after the inclusion of the PTSD diagnosis in DSM-III. Initially, the neuroendocrinology of PTSD was viewed as similar to that of depression. In both PTSD and depression, a number of shared neuroendocrine characteristics were found, such as higher cerebrospinal fluid (CSF) CRH (Bremner et al., 1997) and blunted ACTH response to CRH stimulation (Holsboer, Von Bardeleben, Gerken, Stalla, & Muller, 1984; Smith et al., 1989). However, a number of important differences were also found. In PTSD, hypocortisolism has often been observed compared to controls, which contrasts with the hypercortisolism found in depression (Boscarino, 1996; Mason, Giller, Kosten, Ostroff, & Podd, 1986; Yehuda, Kahana et al., 1995; Yehuda et al., 1990). Furthermore, increased GC-induced suppression of ACTH and an increased number of GRs has been found PTSD, again the opposite of findings in depression (Yehuda, Boisoneau, Lowy, & Giller, 1995; Yehuda, Boisoneau, Mason, & Giller, 1993). The differences were therefore explained by differences in the feedback functioning of the HPA axis. These findings of central hyperactivity, low basal cortisol and increased feedback were initially seen as rather distinct features of PTSD, distinguishing it from depression (Yehuda, 1998).

During recent years there has been a shift in focus, to the inconsistencies in the findings of HPA dysregulations in PTSD, and the potential explanations of this phenomenon (Rasmusson, Vythilingam, & Morgan, 2003; Yehuda, 2002, 2006). However, the paradoxical pattern of hypocortisolism had been introduced to the stress research community, and has since then been given increased attention. Hypocortisolism has been found to be present not only in PTSD but also in some individuals exposed to chronic stress; e.g., parents of fatally ill

children and persons with high work load; and in stress-related disorders; e.g., burnout. chronic fatigue syndrome and chronic pain syndromes. Hypocortisolism has also been observed in disorders with a less well-defefined association to stress, such as in rheumatoid arthritis and atopic disease (Heim, Ehlert, & Hellhammer, 2000). Hypocortisolism has been implicated not only as a mediator between stress exposure and the development of these bodily disorders, but also as an adaptive mechanism with protective functions in chronically stressed individuals (Fries, Hesse, Hellhammer, & Hellhammer, 2005). Relevant to child and adolescent psychiatry, low cortisol has also been found repeatedly in youths with conduct and aggression problems (McBurnett, Lahey, Rathouz, & Loeber, 2000; Oosterlaan, Geurts, Knol, & Sergeant, 2005; Shoal, Giancola, & Kirillova, 2003).

Deviations may be Diurnally Specific

Aside from the total diurnal cortisol secretion (measured through urinary cortisol), dysregulations may differ with respect to the time of day. This is not surprising, considering that the morning cortisol peak is thought to be governed by other mechanisms than the more quiescent periods of the circadian rhythm (Edwards et al., 2001; Schmidt-Reinwald et al., 1999; Wilhelm et al., 2007). Measuring cortisol in saliva or blood allows for examining HPA activity at different time points of the day, while measuring cortisol in urine yields an estimate of the total free cortisol concentration for a defined time period (usually 12h or 24h). See the Measures section for a summary of salivary cortisol measurement.

Several studies have found group differences in basal cortisol to be dependent on the time of day. For example, concerning chronic stress, time-of-day-dependent cortisol relationships have been found with unemployment (higher morning and lower evening cortisol levels) (Ockenfels et al., 1995), financial strain (normal morning and higher evening) (Grossi, Perski, Lundberg, & Soares, 2001) or change in financial strain (decrease in cortisol awakening response, normal evening cortisol levels) (Steptoe, Brydon, & Kunz-Ebrecht, 2005), job strain (higher morning and normal evening) (Steptoe, Cropley, Griffith, & Kirschbaum, 2000), ongoing separation process (normal morning and higher evening) (Powell et al., 2002) and socioeconomic status (normal morning and higher evening) (S. Cohen et al., 2006). Although the results differ, it is clear that sampling several times during the day yields a more thorough picture of basal HPA activity than sampling at a single time point.

Challenges Complement Basal Measurement

In addition to measuring basal HPA activity under non-stress conditions, to enable a view of the short-term HPA axis dynamics challenges may be employed by using different acute stress paradigms. This corresponds to the dual functions and regulations of basal versus stress-induced cortisol levels. Challenge approaches are thus complementary to the measurements under baseline, non-stress, conditions, and some dysregulations may only be evident under HPA axis challenges. In practice, HPA axis parameters are measured at minimum at baseline and after, but often also during the period before and during the challenge. Non-pharmacological challenges aim at mimicking a reallife stressor able to activate the HPA axis, e.g., physical exercise (Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001; Singh, Petrides, Gold, Chrousos, & Deuster, 1999), and psychological/social challenges such as mental tasks and social evaluation (Dickerson & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993), under naturalistic or laboratory conditions. Pharmacological challenges make use of oral or intravenous administration of a substance as the challenge (C. S. de Kloet et al., 2006). E.g., the CRH test involves intravenous administration of CRH, which stimulates the HPA axis via the pituitary. The CRH test is thus used as a measure of the pituitary responsivity to CRH. The dexamethasone suppression test (DST) is a measure of the feedback inhibition at the pituitary level. DST involves oral administration of dexamethasone, a cortisol analogue inhibiting the HPA axis through negative feedback. In response to the DST, ACTH and cortisol levels are expected to be suppressed (C. S. de Kloet et al., 2006).

Social Disadvantage and the HPA Axis in Children

As described above, socioeconomic conditions have a wide range of effects on the health of children and adolescents. Applying a stress model, the HPA axis emerges as a prime candidate for partially mediating these effects. Accordingly, one would expect HPA axis deviations in disadvantaged children and adolescents. But what is the evidence for the HPA axis as a link?

There are only a handful of studies on the subject. Evans and co-workers have found higher overnight cortisol in young children in poor families (Evans & English, 2002) and that the duration of poverty predicted this hypersecretion (Evans & Kim, 2007). Lupien and co-workers (Lupien, King, Meaney, & McEwen, 2000) have found a similar SES difference in morning cortisol levels in 6-10 year old children. However, this SES discrepancy in cortisol levels seemed to diminish in older children (Lupien, King, Meaney, & McEwen, 2001). Higher morning cortisol has also recently been reported in homeless Nepalese boys as compared to squatters (Worthman & Panter-Brick, 2008), although surprisingly middle-class children also displayed similarly high cortisol levels. In contrast, neighborhood level SES has been found to be related to lower cortisol, independently of family level SES (Chen & Paterson, 2006), and one study found no relationship between SES and cortisol (E. Goodman et al., 2005). These two studies with contrasting results, although good sized, only relied on a single cortisol sample that was not standardized to the time of day. One study examining race/ethnicity effects in adolescents, found a flatter diurnal slope, owing to lower morning and higher evening cortisol levels, in adolescents of ethnic minority (DeSantis et al., 2007).

Thus, most studies on socioeconomic conditions and the HPA axis in childhood have found higher cortisol in unprivileged children, although the studies are few. See Table 2 for a summary.

Trauma and the HPA Axis in Children and Adolescents

Traumatic stress in childhood involves a severe threat to the individual, and, considering the common and potentially detrimental short- and long-term impact traumatization confers, an enduring impact on biological stress systems would be expected. The psychobiological effects of trauma have been confirmed in adults with PTSD, where the paradoxical pattern of lower cortisol, hypocortisolism, has been repeatedly observed. But what is the evidence for a dysregulated HPA axis in younger subjects? The literature will be reviewed separately for findings regarding the basal diurnal rhythm (summarized in Table 3), and those regarding acute challenge paradigms.

Table 2. Overview of studies (6 independent samples in 8 papers) examining basal cortisol levels in relationship to socioeconomic or ethnical factors in children and adolescents.

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Reference	Sample (N)	Mean age	Basal cortisol	Relevant findings
		(% girls)	sampling	
Evans & English,	Poor and middle-	Wave 1	Urine	- Wave 1: Higher UFC in poor children,
2002	class, all caucasian	9.2y	12h overnight UFC	relation mediated by cumulative stressors in
	Wave 1 (287)	(49%)		immediate social environment
Evans & Kim,	Wave 2 (207)	Wave 2		- Wave 2: Poverty duration predicted UFC
2007		13.4y		positively
Lupien et al.,	Diverse SES	Subsample	Saliva	- Subsample: Higher cortisol in low-middle
2000	Ethnicity NR	ca 8.5y	0800h and 0900h,	SES than high SES children
	Subsample (217)	(47%)	1 day	- Total sample: Higher cortisol in low SES
Lupien et al.,	Total sample (309)	Tot sample		than high SES children 6-10y; no difference
2001		ca 11y (NR)		12-16y
Worthman &	Nepalese boys (107)	11.8y	Saliva	- Higher cortisol in urban vs rural, homeless
Panter-Brick,	4 subsamples	(%0)	Morning samples,	vs squatters, no difference homeless vs
2008			7-10 days	middle-class
Chen & Paterson,	Diverse ethnicity	16.6y	Saliva	- Cortisol positively related to neighborhood
2006	and SES (315)	(%65)	1 late afternoon	but not individual SES measures
			sample, 1 day	
Goodman et al.,	Diverse ethnicity	16.2y	Blood	- No relationship between cortisol and SES
2005	and SES (758)	(20%)	Early-late morning,	by education
			1 sample	
DeSantis et al.,	Diverse ethnicity	17.1y	Saliva	- Flatter diurnal rhythm (lower morning and
2007	and SES (255)	(75%)	6 samples/day, 3	higher evening cortisol) in ethnic minority
			days	adolescents

SES = Socioeconomic status, UFC = Urinary free cortisol, NR = not reported

Table 3. Summary of studies (17 samples, 20 papers) examining relationships between basal cortisol concentrations and trauma exposure or psychological symptoms related to trauma exposure, in children or adolescents. The studies are organized by main findings (positive, negative or no relationship).

Studies with mainly positive relationships

	(ii) ordinac			20
		(% girls)	sampling	
Carrion et al.,	PTSD (50)	10.7y	Saliva	- Increased cortisol sample 2-4 in trauma
2002	Ctrl (31)	(40%)	4/day, 3 days	subjects
Weems &				- Correlation between PTSS-cortisol:
Carrion, 2007				positive if recent, negative if distal trauma
Cicchetti &	CA (175)	9.3y	Saliva	- No overall difference ctrl vs CA
Rogosch, 2001a	High-risk ctrl (204)	(40%)	0900h/1600h,	- High morning cortisol in multiply and
Cicchetti &			5 days	severely maltreated
Rogosch, 2001b				- Tendency to lower morning cortisol in CPA
				- High morning cortisol in CA INT subjects
				- Low morning cortisol in some EXT
				subgroups (non-CA boys and CA girls)
De Bellis et al.,	PTSD (18)	10.5y	Urine	- PTSD higher UFC vs ctrl
1999	Ctrl (24)	(%08)	24h UFC, 1 day	
Saltzman et al.,	MV (21)	8.3y	Saliva	- Higher cortisol before (and after) an
2005	Clinical ctrl (27)	(29%)	1 afternoon	interview in children exposed to marital
			sample, 1 day	violence
Delahanty et al.,	Acute nIP trauma	13.0y	Urine	- Higher UFC at time of trauma predicted
2005	(20)	(32%)	12h UFC	posttraumatic symptoms (esp. in boys) and
Nugent et al., 2006			Baseline	emotional numbing after 6 weeks

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Studies

Reference	Sample (N)	Mean age	Basal cortisol	Relevant findings
		(% girls)	sampling	
Ostrowski et al.,	Acute nIP trauma	13.4y	12 UFC	- Higher UFC predicted posttraumatic
2007	(38)	(44%)	Baseline + 6v	symptoms after 6 weeks (not 7 months), esp
				in boys and when prior trauma was excluded
Gunnar et al.,	Romanian orphans	Ca 8y	Saliva	- Higher morning cortisol in later adopted
2001	Early (15) and	(48%)	3/day, 3 days	(longer time at orphanage) children
	Late (18) adopted			- Evening cortisol correlated positively with
	Ctrl (27)			time at orphanage for late adopted
Bevans et al.,	Students (68)	10.7	Saliva	- Higher morning cortisol if recent trauma
2008		(46%)	0800h, 1445h,	- Higher evening and lower morning cortisol
			1 day	if both recent and previous trauma
Murali & Chen,	Students (115)	16.9y	Saliva	- Afternoon cortisol correlated positively with
2005		(62%)	1 late afternoon	frequency of violence exposure
			sample, 1 day	
Pfeffer et al.,	Bereaved by terror	9.5	Saliva	- Bereaved children higher morning and
2007	attack (45)	(49%)	0800h, 1600h,	afternoon cortisol
	Ctrl (34)		2100h, 2-4 days	

Studies with mainly negative relationships

Goenjian et al.,	Earthquake (37)	13.5y	Blood	- Lower morning cortisol in adolescents most
1996	5 years after	(38%)	0800h, 1600h,	severely exposed (no difference in afternoon
			2300h, 1 day	or evening cortisol)
King et al., 2001	Recent CSA (10)	6.4y	Saliva	- Lower late morning cortisol in abused
	Ctrl (10)	(100%)	Ca 1000h, 1 day	children

Studies with no significant relationship

Relevant findings		- No difference between CSA and Ctrl		- No difference between PTSD and Ctrl		- No relationship between cortisol and either	severity of exposure or symptoms	- No cortisol difference			- No cortisol difference	
isol	sampling	Urine	24h UFC, 3 days	Blood	0800h, 1 day	Blood	0900h, 1 day	Blood	3 samples ca	1715h, 1 day	Blood	3 comples on
Mean age	(% girls)	11.2y	(100%)	16.2y	(%98)	14.0y	(20%)	9.8y	(54%)		10.2y	(7009)
Sample (N)		CSA, 20	Ctrl, 22	4 PTSD (14)	Ctrl (14)	Earthquake (64)	6.5 years after	MD+CA (13)	MD-CA (13)	Ctrl (13)	MD+CA (10)	MD CA CIV
Reference		s et al.,	1994	al., 200		Goenjian et al.,	2003	Kaufman,	Birmaher, Perel et	al., 1997 Ctrl (13)	Kaufman et al.,	1008

controls, MV = Marital violence, CA = Child abuse, CSA = Child sexual abuse, CPA = Child physical abuse, nIP = non-PTSD = Posttraumatic stress syndrome, PTSS = Posttraumatic stress symptoms MD = Major depression, Ctrl = healthy interpersonal, UFC = Urinary free cortisol, INT = Internalizing symptoms, EXT = Externalizing symptoms.

0745, 1 day

Basal Cortisol Measures

Studies examining the association between basal, i.e. not provoked, measures of cortisol and traumatic events, PTSD or post-traumatic symptoms (PTSS), have most often yielded positive results (see Table 3). However, they differ somewhat in detail. Regarding the direction of association, most studies have found a positive relation between cortisol and either trauma exposure (Carrion et al., 2002; Cicchetti & Rogosch, 2001a; Gunnar, Morison, Chisholm, & Schuder, 2001; Pfeffer, Altemus, Heo, & Jiang, 2007; Saltzman, Holden, & Holahan, 2005), PTSD diagnosis (De Bellis et al., 1999), trauma-related symptoms (Cicchetti & Rogosch, 2001b) or the number of violent events (Murali & Chen, 2005). Studies of acute non-interpersonal trauma (mainly car accidents) have found peritraumatic cortisol levels to be positively predictive of later PTSS (Delahanty, Nugent, Christopher, & Walsh, 2005; Nugent, Christopher, & Delahanty, 2006; Ostrowski, Christopher, van Dulmen, & Delahanty, 2007; Pervanidou et al., 2007).

Three papers, from two samples, by Cichhetti & Rogosch (2001a; 2001b; 2007) require special attention due to large sample sizes (N = 380-677), good design and complex results. They have enrolled children attending a day camp research program for maltreated and non-maltreated low-income disadvantaged children. Saliva collection for cortisol was done in the morning (0900h) and afternoon (1600h) for five days, and additional information was collected from social services records, and questionnaires completed by the camp counselors and by the children themselves. Cicchetti & Rogosch (2001a) report similar cortisol levels in maltreated versus nonmaltreated children, but with cortisol differences within the maltreated group. Most compelling was the high morning cortisol in the subgroup exposed to both sexual and physical abuse. Cortisol was also positively related to the severity of sexual abuse, and there was a tendency of lower morning cortisol in the physically abused children.

Cicchetti & Rogosch (2001b), using the same sample as in Cicchetti & Rogosch (2001a) but including psychopathology data, found a complex interaction of maltreatment exposure, clinical-level symptoms and gender. Maltreated children with internalizing problems had higher cortisol while externalizing cases tended to have lower cortisol, although the latter finding depended on maltreatment exposure and gender. This influence of type of symptoms is analogous to what has been found regarding cortisol and externalizing problems in other studies (McBurnett et al., 2000; Oosterlaan et al., 2005; Shoal et al., 2003). In a similar but separate sample, Cicchetti & Rogosch (Cicchetti & Rogosch, 2007) also examined resilience as a function of maltreatment exposure and cortisol. They found an interaction between maltreatment and cortisol, where cortisol was negatively related to resilience in nonmaltreated and in sexually abused children, but positively related to resilience in physically abused children.

Three other studies found mainly a negative relationship between trauma and cortisol. In one study lower morning cortisol was found in sexually abused girls (King, Mandansky, King, Fletcher, & Brewer, 2001), as was the case in two studies of adolescents exposed to an earthquake in Armenia (Goenjian et al., 2003; Goenjian et al., 1996). These studies only used a single basal sample for morning cortisol. Of studies with negative results regarding basal cortisol (De Bellis et al., 1994; Duval et al., 2004; Kaufman, Birmaher, Perel et al., 1997; Kaufman et al., 1998), all have either used a single cortisol sample (as a part of a challenge paradigm), or 24 h urinary free cortisol, possibly masking deviations specific for a part of the diurnal cortisol rhythm.

Of the studies with positive findings, some were designed to examine different parts of the cortisol diurnal cycle, i.e., at least two samples per day. The three papers by Cicchetti & Rogosch (2001a; 2001b; 2007) described above all found primarily (positive) associations with morning, but not afternoon cortisol levels. Similarly, Gunnar and co-workers (Gunnar et al., 2001) found high morning, but not noon or evening cortisol, in children adopted from Romanian orphanages, although they did find evening cortisol to correlate positively with the time spent in institution. In contrast, one of the studies by Goeniian et al. (1996) found lower morning cortisol in the more highly traumaexposed and symptomatic adolescents. In a study of children suffering parental death from the September 11 terror attacks, a nonspecific increase in both morning and afternoon cortisol was found (Pfeffer et al., 2007). One study of pediatric PTSD found higher cortisol in the late morning to evening part of the day, with no difference in the early morning, as compared to controls (Carrion et al., 2002). However, morning cortisol interacted with time since the most recent trauma in its relation to PTSD symptoms: in children exposed to recent trauma (< 12 months) cortisol correlated positively with symptoms, while in children exposed to distal trauma (>12 months) cortisol correlated negatively with symptoms (Weems & Carrion, 2007). Related to this, a recent study in a community sample of school children reports an interaction between recent (<12 months) and previous (>12 months) trauma exposure, where children with high frequency of recent trauma displayed higher morning cortisol. In contrast, those with high frequency of both recent and previous trauma exposure displayed a lower morning as well as higher afternoon cortisol (Bevans, Cerbone, & Overstreet, 2008).

A few studies have measured ACTH simultaneously with cortisol. Two of these found lower basal ACTH, coupled with normal cortisol (in sexually abused girls (De Bellis et al., 1994) and adolescents exposed to an earthquake (Goenjian et al., 2003)), while two found no basal ACTH group differences (Duval et al., 2004; Kaufman, Birmaher, Perel et al., 1997). It should be noted that all these ACTH measurements were done exclusively as a part of challenge paradigms and thus were not primarily designed to measure basal ACTH levels.

Challenge Studies

Of the studies conducted on children and adolescents exposed to trauma, four studies have used the DST. In children bereaved by a terrorist attack, suppression was found to be dependent on psychiatric disorder (greater suppression in PTSD; lower in generalized anxiety disorder (GAD), as compared to not bereaved controls) (Pfeffer et al., 2007). Greater ACTH suppression with no difference in cortisol suppression was found in sexually abused adolescents with PTSD (Duval et al., 2004). One study of traumatized adolescents with PTSD found no difference in cortisol suppression, as compared to traumatized non-PTSD children and to healthy controls (Lipschitz et al., 2003). Another study (which did not examine ACTH suppression) found a greater cortisol suppression in more severely traumatized adolescents, living closer to the epicentre of an earthquake (Goenjian et al., 1996). Goenjian and coworkers also examined the cortisol and ACTH response to physical exercise, in a separate adolescent sample exposed to the same earthquake (Goenjian et al., 2003). They found no difference in the ACTH or cortisol responses between the high- and low-exposed subjects.

Two studies have employed the CRH challenge. One found an attenuated ACTH response to CRH administration, with no cortisol difference, in sexually abused girls (De Bellis et al., 1994). The other study examined abused and non-abused children, all with major depression (MD) (Kaufman, Birmaher, Perel et al., 1997). They found an increased ACTH, coupled with normal cortisol response to CRH in the abused children with depression, compared to depressed non-abused and control children. Another study with similar design by Kaufman and co-workers (Kaufman et al., 1998), found no difference in the cortisol response to a serotonin challenge between depressed abused, depressed non-abused and control children.

One study examining the cortisol response to an arithmetic and social-evaluative task in high school students found no relation to previous violence exposure (Murali & Chen, 2005), despite an association between violence exposure and basal cortisol secretion.

Summary of the Literature

The literature focusing on the HPA axis in children and adolescents who have experienced trauma is inconclusive. Since most (published) studies display positive results, HPA axis activity seems to be connected to trauma exposure or to symptoms thereof. However, with respect to the fundamental details the results differ, e.g. the direction of association and which part of the diurnal cycle is affected.

Regarding basal levels, the most common finding is that basal cortisol, primarily in the morning, is positively related to trauma exposure or trauma-related symptoms in children and adolescents. There are however discrepant

results and indications that the results may be dependent on trauma characteristics and psychological symptom dimensions. Regarding dynamic challenges, both increased, decreased and normal ACTH responses have been found in relation to trauma, with mostly negative results regarding the cortisol response. Aside from other methodological differences between the few existing studies, the type of challenge (pharmacological, psychological or physical) varies greatly, which further makes it difficult to draw firm conclusions.

Obsessive-Compulsive Disorder and the HPA axis

As described above, children with OCD experience more daily stress than their healthy peers, and there are several tentative indications that the HPA axis, as in depression, may play a role in the pathophysiology of the disorder. Again, this would require that the HPA axis is affected in children with OCD.

However, to the author's knowledge no studies except Paper II have examined cortisol levels in children and adolescents with OCD. Cerebrospinal fluid (CSF) CRH has been examined in young patients with severe OCD, and although no relation to symptoms was found (Swedo et al., 1992), CRH levels have been shown to decrease following pharmacological treatment (Altemus et al., 1994). A smaller pituitary volume has been found in young OCD subjects related to compulsive, but not obsessive, symptoms (MacMaster, Russell, Mirza, Keshavan, Banerjee et al., 2006). This could be indicative of an HPA axis dysregulation. In contrast, and interestingly enough, the same research group has observed an enlarged pituitary in young depressed patients (MacMaster, Leslie, Rosenberg, & Kusumakar, 2008; MacMaster, Russell, Mirza, Keshavan, Taormina et al., 2006). Thus, the evidence for HPA axis dysregulations in children with OCD so far is weak.

Due to the limited pediatric literature, let us look into the findings in adults, to yield a surrogate picture of the HPA axis in young people with OCD. Interestingly, some similarities can be discerned between the HPA axis in adults with major depression (MD) and adults with OCD: basal hypersecretion of CRH (Altemus et al., 1992), ACTH (Kluge et al., 2006) and cortisol (Catapano, Monteleone, Fuschino, Maj, & Kemali, 1992; Kluge et al., 2006; Monteleone, Catapano, Del Buono, & Maj, 1994; Monteleone, Catapano, Fabrazzo, Tortorella, & Maj, 1998; Monteleone et al., 1995). Basal cortisol has also been shown to correlate to clinical (although not specifically obsessive/compulsive) symptoms in OCD patients (Millet et al., 1998). The HPA level of dysregulations is unclear; some have found blunted ACTH and normal cortisol response to dynamic CRH challenge (Bailly et al., 1994), pointing towards a pituitary dysfunction, while simultaneous hypersecretion of ACTH and cortisol (Kluge et al., 2006) indicates a central HPA hyperactivity under basal conditions. The cortisol levels in OCD have, however, been found to be resistant to clinically successful treatment (Millet et al., 1999; Monteleone et al., 1995),

contrary to MD patients where cortisol levels usually decrease after successful treatment (Gillespie & Nemeroff, 2005). This has led to the hypothesis of HPA dysfunction as a trait rather than as a state marker of OCD. Nonsuppression in the DST, a common feature of MD (Gillespie & Nemeroff, 2005), is also displayed in some OCD subjects, independently of depressive diagnosis or symptoms (Catapano, Monteleone, Maj, & Kemali, 1990; Cottraux, Bouvard, Claustrat, & Juenet, 1984). Still, there are inconsistencies in the literature, both regarding the hypersecretion of CRH (Chappell et al., 1996) and of cortisol (Atmaca, Tezcan, Kuloglu, & Ustundag, 2005; Hollander et al., 1998; Millet et al., 1999).

AIMS

Several aspects of stress in childhood have been insufficiently studied. The general aim of this thesis was to examine the relationship between different forms of psychosocial stress, mental health and cortisol, as a marker for HPA axis activity, in children and adolescents living under ordinary and adverse conditions. The aim of each paper was:

Paper I

To examine the relationship between factors of psychosocial stress and diurnal salivary cortisol levels in school-aged children.

Paper II

To compare salivary cortisol levels between youths with OCD and a reference group of school children, with respect to the diurnal secretion as well as the response to an acute stressor. A second aim was to examine the relationship between cortisol levels at baseline, and obsessive-compulsive symptoms severity at intake and after 6 months.

Paper III

To examine the association between cortisol levels at different times of the day, and trauma-related symptoms and sense of coherence, in adolescents exposed to childhood maltreatment.

Paper IV

To study specific relationsships between sociocultural conditions, traumatic events (interpersonal and non-interpersonal), and psychiatric symptoms (externalizing and internalizing) in school-aged children.

Paper V

To explore the influence of polytraumatization on psychological symptoms, and examine gender patterns in the effects of interpersonal and non-interpersonal events on psychological symptoms, in children and adolescents.

METHODS

Participants and Procedures

The papers in the present thesis originate from five data collections, as overviewed in Table 4. The data was collected cross-sectionally. The general procedure in the studies was as follows; for details, see the relevant paper.

The head of the schools, residential care homes and OCD out-patient clinic was contacted about participating in the respective study. Written information about the purpose and procedures was given to the staffs and to the eligible families. Written informed consent was given by parents and in the two adolescent samples, also by the adolescents themselves. Questionnaires and saliva collecting tubes were distributed to the participants. Questionnaires were completed at home, except for the adolescent school sample where they were completed in school, and collected by the research staff or returned by mail. Salivary sampling was done at the schools and at home (school-age sample), at the residential care homes (traumatized adolescents) or at home (OCD sample). Saliva sampling was done at three time points: in the early morning (0830h), late morning (1030h) and in the evening (about 2100h), for 2-4 consecutive days. In the school-aged and traumatized adolescent samples, sampling was done during weekdays and, in the OCD sample, during weekends.

Table 4. Summary of samples. *N* varies between analyses due to non-response. See text for details.

School samples	Age,	Total N	Main measures	Presented in
	years	(participation)	used	paper
School-aged	6-12	273- 336	Basal cortisol	I, II
children,		(65-81%)	Demographics	
First year			SDQ	
School-aged	6-12	240-270	Cortisol response	II, IV, V
children,		(64-72%)	Sociodemographics	
Second year			SDQ	
			LITE	
Adolescents	12-20	400	LITE	V
		(89%)	TSCC	
Clinical samples	Age,	Total N	Main measures	Presented in
	years	(participation)	used	paper
Traumatized	13-19	15	Basal cortisol	III
adolescents		(94%)	TSCC	
			SOC	
Children	9-17	23	Basal cortisol	II
with OCD		(70%)	Cortisol response	
			Clinical evaluation	

SDQ = Strengths and difficulties questionnaire, LITE = Life incidence of traumatic events, TSCC = Trauma symptoms checklist for children, SOC = Sense of coherence, OCD = Obsessive-compulsive disorder

School-age Sample

Data was collected at two elementary schools as a part of a larger project concerning stress, health and outdoor education in school children. Aspects of the outdoor education program are reported elsewhere (Gustafsson, Szczepanski, Nelson, & Gustafsson, 2008). Questionnaires were completed by parents (basic information and a symptoms questionnaire, the SDQ, see Measures) and teachers (SDQ). Salivary samples were collected at home and at the schools during four days (4 early morning, 3 late morning and 3 evening samples).

The first year informed consent was obtained from the parents of 342 out of 417 children, 164 boys and 176 girls. Due to non-response on one or more measures, the numbers differ between analyses. In Paper I, at least one cortisol sample was collected for each time point for 332 children (80%) and with complete additional sociodemographic and psychiatric symptoms data from 273 children (65%). In paper II, the same basal cortisol data was used but for each sample time, thus N varies between 333 (2100h sample) and 336 (0830h sample).

One year later, the procedure was repeated for both schools, with some differences. A questionnaire about traumatic life events (LITE, see Measures) experienced by the children was distributed to the parents. The SDQ was completed by parents but, due to non-compliance, not by teachers. In addition, the cortisol response to a fire alarm was measured. This had been pilot tested in the first data collection. The second day, the 1030h sample was used as a pretest sample. At 1045h a fire alarm was initiated and a fire drill was executed. As the bell rang, the children went outside under supervision of their respective teacher, and then returned to their classrooms. At 1115h, a post-test cortisol sample was collected.

The second year, 376 children were available at the two schools, and informed consent was collected from 315 of them. In Paper V, only the traumatic life events questionnaire was considered, which was available from 270 children (72%), 135 boys and 135 girls. Since both the sociodemographic, traumatic life events and symptoms information were necessary for the main analyses in Paper IV, 57 children were excluded due to non-response with a final N of 258 (69%). In Paper II, all children with both pre-test and post-test cortisol samples were included as a comparison of acute stress, N = 240 (64%).

Adolescent Sample

This sample was collected as a part of a project focusing on traumatic stress and dissociation in adolescents (Nilsson, 2007). The intent was to study adolescents ranging from 13 to 19 years from different socioeconomic areas in the city of Linköping. The selection was based on grades and divided into two grade groups; one of grade 7-9 of compulsory school representing early adolescence, and one of grade 2 in secondary school representing late adolescence.

Out of all compulsory schools in Linköping and clustered by socioeconomic areas in the city, four schools were randomly chosen. From these, three classes from each of the grades 7, 8 and 9 were randomly chosen (9 classes in total). All schools who were offered participation agreed to do so. From all secondary schools 5 classes from different educational programs were randomly chosen, to cover pupils from different socioeconomic groups. Questionnaires were completed by the adolescents in the schools (LITE and TSCC, see Measures, as well as two dissociation questionnaires reported elsewhere (Nilsson & Svedin, 2006a, 2006b), with the presence of a member of the research staff to answer any questions. Out of 449 adolescents in the chosen classes, 400 (89%) agreed to participate and completed the questionnaires, 279 (146 boys, 133 girls) from the compulsory school and 121 (64 boys, 57 girls) from secondary school.

Traumatized Adolescents

The traumatized adolescents were contacted through two residential care homes for maltreated adolescents with psychosocial and psychiatric problems, one located outside Linköping and one in the town of Västervik. Trauma symptoms (Trauma Symptom Checklist for Children, TSCC), sense of coherence (Sense of Coherence scale, SOC) and traumatic life events (Life Incidence of Traumatic Events, LITE) questionnaires were completed by the adolescents the same week as the saliva sampling. Sixteen adolescents were offered participation and 15 agreed (94%), 14 girls and one boy.

Children with Obsessive-Compulsive Disorder (OCD)

The data collection was conducted at the OCD/Anxiety Clinic, Queen Silvia's Children Hospital in Gothenburg, as a part of a larger ongoing project concerning the long-term outcome of OCD in childhood. Data was collected consecutively. Clinical assessment was done at the clinic. The first weekend saliva samples were collected (2 early morning, 2 late morning and 3 evening samples) and were sent by mail the following Monday to the laboratory.

The week after the basal cortisol sampling, an exposure treatment session was conducted as a part of a cognitive behavioral therapeutic paradigm, together with a therapist. During the session, the child confronted the focus of his/her anxiety, and rated his/her anxiety. One salivary cortisol sample was taken before, and one 30 minutes after the exposure, as a measure of the pretest-posttest cortisol response.

Thirty-three children and their families were asked to participate, and 23 (70%) agreed to participate (10 boys, 13 girls). One child did not complete both response samples. All children were of normal intelligence, had OCD as their main diagnosis, and the majority of the sample (n=17, 74%) had one or more comorbid diagnoses.

Measures

Salivary Cortisol – Paper I, II, III

The measurement of salivary cortisol

Previously, cortisol has been measured solely by sampling of blood or urine. During the recent decades techniques to collect and measure low cortisol levels in saliva have been developed for adults and older children (Aardal-Eriksson, 2002; Kirschbaum & Hellhammer, 1994) as well as for infants (Mörelius, 2006).

Several advantages with salivary compared to blood or urine cortisol measurement have been mentioned in the literature (Kirschbaum & Hellhammer, 1994; Lewis, 2006). It is noninvasive and stress-free, which is important in studies of stress, since the anticipation of blood sampling can activate the HPA axis. This is also especially valuable when studying children, making research more ethically appealing and allowing for multiple sampling. The ease of saliva collection also makes it possible for sampling at home, and is more convinient than urine collection. Salivary cortisol, like serum cortisol, has the advantage over urine cortisol in that serial samples can be taken to discern real-time levels (e.g., time-of-day differences or pre-post-stress levels), whereas urine cortisol only gives a measure of total cortisol secretion over a time period (e.g., 12 or 24 hours).

Salivary cortisol is highly correlated with the active free (i.e., not bound to plasma proteins) fraction of cortisol in serum (Kirschbaum & Hellhammer, 1994). Cortisol, being a small, neutral, lipophilic molecule, enters the saliva through passive diffusion through the salivary gland epithelium (Quissell, 1993). Saliva secretion and its protein/fluid content are influenced by stress through the autonomous nervous system (Baum, 1993). The salivary cortisol concentration is, however, not influenced by salivary flow rate or protein content (Aardal-Eriksson, 2002; Kirschbaum & Hellhammer, 1994; Umeda et al., 1981).

Salivary cortisol seems to be stable at room temperature for about one week (Aardal & Holm, 1995; Whembolua, Granger, Singer, Kivlighan, & Marguin, 2006), and at -20°C for about one year (Aardal & Holm, 1995; Garde & Hansen, 2005). The effect of freezing and thawing is inconclusive (Aardal & Holm, 1995; Garde & Hansen, 2005), but temperature variations during five days (simulating mailed samples) do not seem to affect the cortisol levels (Clements & Parker, 1998). Since cortisol is present in much higher (roughly 50 times) levels in serum than in saliva, blood contamination due to minor wounds in the oral mucosa may interfere with the analysis. It has been indicated that this is only a small methodological problem in field studies of salivary cortisol (Granger et al., 2007; Kivlighan et al., 2004).

Salivary cortisol in this thesis

Essentially the same procedure of saliva collection, handling and analysis was used in the different samples. Saliva was collected using a commercial Salivette plastic test tube consisting of an absorbent cotton roll, a plastic roll retainer and a centrifuge tube. The following written and oral instructions were given to the participants: the hour before sampling, they were to engage in calm activities, and no food or drink intake (except water), tooth brushing or chewing gum was allowed. Fifteen minutes before sampling, the participants rinsed their mouths with water. The cotton wool swab was then inserted into the mouth without touching it with the fingers, and moved around in the mouth for 2-3 minutes. Then the swab was spitted out back into the tube, again without touching it with the fingers. The sampling procedure was supervised by the teachers (day samples) and parents (evening samples) in the school-age sample, by the parents (basal sampling) and psychiatric staff (response sampling) in the OCD sample, and by the residential care home staff in the traumatized adolescent sample.

The saliva samples were then transported to the laboratory by the research staff (school-age sample and traumatized adolescents sample), or sent to the laboratory by mail (OCD sample). In the school-age sample, the children brought the evening sample to the school the next day, to be collected by the research staff. The transportation was done the same day as the sampling or 1-2 days after. No sample arrived at the laboratory later than 5 days after the sampling was completed. Upon arrival at the laboratory, the samples were centrifuged (at $1500 \times g$, 3000rpm) and then kept in the freezer (- 20°C) for up to six months before they were analyzed.

On the day of analysis, the samples were brought to room temperature, and analyzed using an Enzyme Immunoassay (EIA) kit (Salimetrics LLC, 2008), at the Laboratory for Clinical Chemistry, Linköping University Hospital. The technique is developed specifically for the measurement of salivary cortisol, and the test principle is as follows: Cortisol in standards and unknowns (the study samples) are added to a 96-well microtitre plate, pre-coated with monoclonal anti-cortisol antibodies. During incubation, the cortisol in standards and unknowns competes with cortisol linked to horseradish peroxidase for the antibody binding sites, and then unbound components are washed away. Tetramethylbenzidine (TMB) is added, and the bound cortisol peroxidase catalyzes a reaction of the TMB, generating a blue color. The reaction is stopped by adding sulfuric acid, generating a yellow color. Optical density is then measured at 450 nm. The amount of bound cortisol in the study sample is inversely related to the amount of cortisol peroxidase.

Upon the detection of unexpectedly high concentrations, the sample was checked for blood contamination. No sample was discarded in this way. As has been pointed out by others, blood contamination in salivary is not a large problem in salivary cortisol measurement in children (Granger et al., 2007).

Total precision of the method was CV (coefficients of variation) = 14.4% at 3 nmol/L and CV = 8.5% at 25 nmol/L (N = 368). The lower detection limit was 0.4 nmol/L and the higher detection limit was 50 nmol/L. Still, the numerical value was used in data analyses even for measured concentrations outside this range, since the scale level otherwise would be reduced to ordinal, and this approximation was deemed preferable for research purposes. Of all salivary samples across the studies (N = 3997), 197 samples (4.9%) were below 0.4 nmol/L, most of these were evening samples. These were all included in the analyses using the estimated concentrations, since a lower precision was deemed preferable to excluding a large portion of the evening samples or using a cut-off value and thus changing the scale level. Only three samples with cortisol concentrations >50 nmol/L were reported in the school-age sample, and none in the other study samples. Of these, two were coupled with consistently high cortisol levels for that individual (the majority of samples outside 2 SD). One single sample was measured to 172 nmol/L and all other samples for that individual were <3 nmol/L. This unexpectedly high concentration sample was discarded since we could not exclude any methodological problems.

The mean cortisol concentration was calculated for the time of day, and used as the main dependent variables in Paper I, II, and III, i.e. early morning (0830h), late morning (1030h) and evening (around 2100h) cortisol values. In the school-age sample the arithmetic means were calculated from a maximum of four samples in the early morning and three samples in the late morning and evening; in the traumatized adolescents from three samples at each time of day; and in the OCD sample from three evening samples and two early morning and late morning samples. Each participant was considered a valid case if at least one sample from the respective time of day was present. In Paper I and III the area under the curve (AUC) was also calculated and used as a dependent variable, as a rough measure of total basal cortisol secretion. The formula for AUC with respect to ground was used (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003), with the unit nmol/L×h. The mean of the AUC from the three days was used as dependent variable in Paper I and III.

Background Information and Sociodemographics – Paper I, IV

The parents completed a questionnaire about the children's health (chronic illness of the child and glucocorticoid medication), family structure (number of siblings and birthorder, parental separation and who the child lived with) and demographics (the parents' age, education, occupation and country of origin). Children with medical conditions or topical glucocorticoid medication did not differ in cortisol levels from the rest of the children, and were included in the analyses.

Occupation was used as the principal measure of socioeconomic status (SES), and was coded according to the Swedish Socioeconomic Classification

(Statistics Sweden, 1984). This yields seven main levels: 1) unskilled workers, 2) skilled workers, 3) assistant non-manual employees, 4) intermediate non-manual employees, 5) non-manual employees at higher levels, 6) self-employed people and 7) farmers, plus unemployed. The highest occupational level of the parents was used as a measure of family SES or social class.

In Paper I, a dichotomous measure was used, with the lowest SES group (unskilled workers) plus unemployed contrasted to the rest, as a component of a cumulative index of SES, immigrant family and social impairment due to psychiatric symptoms (from the SDQ, below). In paper IV, the more detailed seven-graded scale plus unemployed was initially used with some merging of categories. The self-employed level, being a very heterogeneous group, was merged with the other categories based on education and occupation of the other parent. Then, levels 4 and above were collapsed, and the unemployed were included as a separate, lowest, level. This yielded a five-level measure of family social class (FSC).

Parental country of origin was used as a measure of immigrant family or ethnic minority status. The child was considered belonging to an immigrant family if at least one parent was born outside Scandinavia.

Education, although not used in the main analyses, was coded on a four-graded scale based on the highest attained degree: 1) university/college, 2) theoretical secondary school, 3) practical secondary school and 4) basic education.

Life Incidence of Traumatic Events (LITE) – Paper III, IV, V

LITE (Greenwald & Rubin, 1999) is a short screening checklist concerning lifetime exposure to traumatic events, translated into Swedish (Larsson, 2003a, 2003b). Both a self-report (LITE-S) for older children and a parent-informant (LITE-P) version is available; LITE-P was used in the school-age sample and LITE-S in the adolescent samples (non-clinical and traumatized). The checklist consists of 15 items describing traumatic events, and one open item ("Have you experienced another scaring or upsetting event?"). Each item asks for the experience of one specific event (yes/no), with questions about how many times the person has experienced the event, how old he/she was the first time, how upsetting/disturbing he/she appraised the event at the time, and how upset he/she finds the event at present. Since the objective exposure to different traumatic events was the focus of the papers in this thesis, only the incidence (yes/no) data was used.

LITE-S has displayed an adequate three-week test-retest reliability (Spearman's rho = .76 for the total number of events), among a subsample of the adolescents in Paper V (n = 84) (Nilsson, Gustafsson, & Svedin, in press). The LITE-P has not been psychometrically evaluated yet. The face validity of LITE is considered adequate, since the questions are simple and the selection both

covers more common and more severe types of events, which still can not be considered normative.

There is no established and standardized way to score LITE. In this thesis, three different levels of trauma exposure variables were used: 1) the incidence of each event, 2) the number of different interpersonal (IP) and non-interpersonal (nIP) events, respectively, and 3) the total number of different events (polytraumatization, PT). Thus, the three levels of exposure variables correspond to a decreasing degree of stressor specificity.

Strengths and Difficulties Questionnaire (SDQ) – Paper I, IV, V

The SDQ (R. Goodman, 1997, 1999) is a short screening instrument for child and adolescent psychiatric symptoms, present in several versions. In this thesis, the Swedish translations of the extended parent- and teacher-informant versions were used (SDQ-Swe) (Smedje, Broman, Hetta, & von Knorring, 1999). The SDQ consists of 25 principal items (10 positive and 15 negative) concerning different aspects of behavioral and emotional symptoms. The items are marked (coded) as "never" (0), "somewhat true" (1) or "certainly true" (2). The items are added up in four negative subscales (emotional symptoms, conduct problems, hyperactivity-inattention and peer problems) summarized in total difficulties score, and one positive subscale (prosocial behavior). The extended version also includes 3 (teacher version) to 5 (parent version) questions about social impairment due to any symptoms, in the domains of home, friendships, classroom performance and leisure activities, summed up separately (impact). Thus, in total seven variables are generated.

The SDQ, with parents and teachers as raters, has been evaluated in a number of countries in Europe (Becker, Woerner, Hasselhorn, Banaschewski, & Rothenberger, 2004; R. Goodman, 2001; Klasen et al., 2000; Obel et al., 2004; Woerner, Becker, & Rothenberger, 2004), the U.S. (Bourdon, Goodman, Rae, Simpson, & Koretz, 2005), and in other countries (Alyahri & Goodman, 2006; Du, Kou, & Coghill, 2008; R. Goodman, Renfrew, & Mullick, 2000; Samad, Hollis, Prince, & Goodman, 2005), and has generally been found to have acceptable reliability and validity. The psychometric properties of the parent version of SDQ-Swe has been evaluated in two studies (Malmberg, Rydell, & Smedje, 2003; Smedje et al., 1999) and the postulated five-factor structure has been confirmed in the SDQ-Swe (Smedje et al., 1999). The teacher version has not been evaluated in Sweden.

For Paper I, both teachers and parents SDQ reports were available. Of these, the teacher version was chosen to yield a measure independent from from the parent reports of sociodemographics. The impact score was chosen since it represents symptoms in a psychosocial context. To include it as one factor of a cumulative index of psychosocial stress, the score was dichotomized. The cutoff of 2 or more was chosen (R. Goodman, 1999), meaning that the child had to

have severe distress or impairment in one domain or moderate impairment in two domains. This cut-off may thus be tending to identify the most severely impaired children.

Paper IV and V were based on the data from the second year of the schoolage sample, where only parent reports were available. In Paper IV, contrasting dimensions of mental health were of interest for examining outcome specificity. Broadband measures of internalizing/emotional and externalizing/behavioral problems were chosen since the distinction is well-known and –used, and thus allows for comparisons to other studies (McMahon et al., 2003). The emotional symptoms (ES) and conduct problems (CP) scores were used as approximations of internalizing and externalizing symptoms dimensions, respectively. These subscales have been shown to correlate rather strongly (r = .60 - .84) to the corresponding dimension of the Child Behavior Checklist (Achenbach, 1991; R. Goodman & Scott, 1999; Klasen et al., 2000).

Paper V, also based on the second year of the school-age sample, focused on traumatic events and polytraumatization, and the total difficulties score was used as the outcome measure.

Trauma Symptom Checklist for Children (TSCC) – Paper III, V

TSCC (Briere, 1996) is a self-report questionnaire designed to capture traumarelated symptoms in older children and adolescents. It consists of 54 items, each marked on a four-point Likert scale: 0 "never", 1 sometimes", 2 "lots of times" and 3 "almost all of the time". The items are summed up to form a total score, as well as six clinical subscales: anxiety, depression, posttraumatic stress, sexual concerns, dissociation, and anger. Sexual concerns and dissociation are divided into additional subscales (sexual preoccupation and sexual distress, and fantasy and overt dissociation, respectively). The TSCC also includes two validity scales, underresponse and hyperresponse, which consider the child's tendency to deny symptoms or overrespond to the items.

TSCC has been evaluated in the U.S., and have found to display adequate psychometrical properties (Briere, 1996; Crouch, Smith, Ezzell, & Saunders, 1999; Sadowski & Friedrich, 2000). The psychometrics of TSCC has also been evaluated for Swedish children and adolescents, including a normative group (N = 728) and a clinical group with known sexual or physical abuse history (N = 91) (Nilsson, Wadsby, & Svedin, 2008). The internal consistency, 3-week testretest reliability and construct validity were all satisfactory. The criterion validity was good with consistent differences between normative and clinical groups for all clinical subscales, and, except for sexual concerns, for trauma-exposed versus not trauma-exposed subjects in the normative group.

In Paper III, the six clinical subscales were reduced to three dimensions: internalizing (the mean of depression and anxiety subscales), externalizing (anger subscale) and post-traumatic (post-traumatic symptoms, sexual concern

and dissociation). This was done for several reasons. Cortisol has been shown to differ substantially with respect to symptom dimension in traumatized children (Cicchetti & Rogosch, 2001b), which is why we found it interesting to report results by categories of symptoms rather than just the total score. Still, the sample size was low and to reduce the problem of mass significance, we decided that using all six subscales would create too detailed an analysis. Thus, the compromise of combining the subscales into fewer dimensions was chosen.

In Paper V, the total score of TSCC was used as a general measure of mental health and post-traumatic symptoms in adolescents.

Sense of Coherence (SOC) scale – Paper III

Sense of coherence is a concept developed by Antonovsky, based on his salutogenic model of health (Antonovsky, 1979, 1987). The salutogenic model is based on the assumption that stress is an integral part of life. It focuses on the mechanisms leading to health (salutogenesis) rather than to disease (pathogenesis), and health is viewed as a continuum rather than dichotomous. Sense of coherence is conceptualized as a global, pervasive and enduring but dynamic orientation of confidence concerning the demands and challenges of life, and comprises three components. 1) Comprehensibility: to what degree the demands are ordered, predictable and understandable, 2) Manageability: the extent to which resources are available to handle the demands, and 3) Meaningfulness: a motivational component, to which degree the demands are viewed as challenges worthy of investment and engagement (Antonovsky, 1987).

SOC is operationalized in the SOC scale (Antonovsky, 1987), which exists in several different versions across the world. The Swedish translation of the SOC-29 was used in the present thesis. It consists of 29 items, rated on a 1 to 7 graded Likert scale, which are summed up to generate total SOC.

The internal consistency have consistently been found to be adequate (reviewed in Antonovsky, 1993; Eriksson & Lindstrom, 2005), including among Swedish adolescents (Hansson & Cederblad, 1995). The SOC-29 has generally been shown to be rather stable (Antonovsky, 1993; Eriksson & Lindstrom, 2005), including in Swedish adult samples (Langius, Bjorvell, & Antonovsky, 1992), and Swiss adolescents (Buddeberg-Fischer, Klaghofer, & Schnyder, 2001). Construct validity and criterion validity has been found to be good (Antonovsky, 1993; Eriksson & Lindstrom, 2005; Hansson & Cederblad, 1995; Olsson, Hansson, Lundblad, & Cederblad, 2006).

In Paper III, the total SOC-29 score was used as a measure of sense of coherence.

Clinical Assessment – Paper II

A thorough clinical evaluation was used to assess symptomatology in the OCD sample included in Paper II. Since this evaluation was not the main focus of the paper and the results where negative, it will be mentioned just briefly.

All children where assessed with Wechsler's Intelligence Scale for Children (WISC) (Wechsler, 1999). Psychiatric diagnosis were assessed through the Schedule for Affective Disorders in School-Aged Children – Present and Lifetime version (K-SADS-PL) (Kaufman, Birmaher, Brent et al., 1997), a semi structured diagnostic interview. Obsessive-compulsive symptom severity and characteristics was evaluated with Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997; Storch et al., 2004) a semistructured interview generating a 0-40 scale of symptom severity. CY-BOCS includes a subjective clinical global impression (CGI), rated on a 0-6 scale, of the severity of illness. The overall severity of all symptoms, including comorbid diagnoses, was assessed with Children's Global Assessment Scale (C-GAS), as rated on a 0-100 scale (Shaffer et al., 1983).

Data Analysis

P < .05 was considered statistically significant, and p < .10 a tendency/near-significant. Effect sizes are reported as Pearson's r, ΔR^2 , R^2 or Cohen's d, depending on analysis. Cohen's d was calculated as $d = (M_1 - M_2)/\sqrt{((s_1^2 + s_2^2)/2)}$ (J. Cohen, 1988), or converted from Pearson's r using the formula $d = 2r/\sqrt{(1-r^2)}$ (H. Friedman, 1968). SPSS versions 12.0 - 14.0 were used for all analyses.

Paper I

In Paper I, non-parametric tests were used; Mann-Whitney U test for two independent groups, and Kruskal-Wallis test for several independent groups, with Bonferroni adjusted Mann-Whitney tests as post hoc tests (with all possible comparisons within each analysis, k = 6) to limit the global type I error rate.

Paper II

Differences between groups in cortisol variables were analyzed using separate *t* tests for independent samples. For dependent samples, *t* tests and repeated measures ANOVA were used. Associations between cortisol and clinical measures were examined with correlation analysis (Pearson's *r*).

Paper III

Pearson's product-moment correlation coefficient, r, was used as an estimate of the linear association between the variables.

Paper IV

Hierarchical regression analysis was used, where internalizing (emotional symptoms from the SDQ) and externalizing (conduct problems from the SDQ) symptoms were regressed separately, on gender and age (step 1), family social class and immigrant family (step 2), interpersonal and non-interpersonal events (step 3), and the other symptoms dimension (step 4). Differences between regression coefficients were examined with partial *F* tests and *t* tests.

Paper V

Analyses were carried out separately in the two samples. A series of hierarchical regression analyses were conducted, with psychological symptoms score as the criterion variable, and single life events, nIPE and IPE, and PT as the main predictors. Differences between between regression coefficients were examined with partial *F* tests, using the same method as in Paper IV.

Ethical Considerations

All studies were approved by the local research ethics committee. Written and oral information about the studies was given to all participants. The voluntary nature of participation, and the possibility to terminate participation at any time, was emphasized to ensure the autonomy of the children and parents. Written informed consent was collected from all children, and/or their legal guardians. Movie tickets were given to the children in the clinical samples as a symbolic reward for participation. The identities were coded upon data analysis and results only presented on group level, to avoid identification. There were no elements of risk or pain in the studies. Potentially awkward or disturbing elements of the studies were:

- 1) Saliva sampling: the saliva collection is a non-invasive method that is well-used in pediatric samples. It is preferable to invasive methods due to its non-stressfulness. The sampling and storage of biological samples is a potential source of disturbance of the integrity. To ensure the integrity of the participants, the storage and use of the biological samples followed the Act (2002:297) on Biobanks in Health Care.
- 2) Questionnaires: these can be considered as disturbing the integrity of the participants. All questionnaires, or similar questionnaires, have been used previously. The questionnaires have been stored in a research archive.
- 3) Acute stressors: Both the exposure treatment session in the OCD sample and the fire alarm in the school-age sample can be stressful to the children. However, they were part of the treatment program and yearly safety routine, respectively, and not introduced by the research group.

The advantage of increased knowledge about stress and health consequences relevant for all children in Sweden, and also in other countries, should reasonably compensate for the disturbances induced by saliva samples and questionnaires. Likewise, a vulnerable group concerned with child psychiatric care can potentially be given improved contact, on account of increased knowledge.

RESULTS

Paper I

Cortisol varied by the cumulative index of psychosocial stress (0, 1, 2, 3 factors, as examined by the Kruskal-Wallis test), both regarding the AUC (p = .014), early morning cortisol (p = .004) and evening cortisol (p = .012). Post hoc test (Bonferroni-corrected) indicated a difference between the groups where 0 factor vs. 1 factor differed in the AUC (p = .048) and early morning (p = .006) cortisol. The group with all three factors differed from the one with none factor regarding evening cortisol (p = .030). Similarly, children with one or more factor present displayed higher cortisol both in the AUC (p = .003), morning (p < .001) and evening (p = .029).

Considering that the groups with 1-2 factors displayed similar cortisol concentrations, data were collapsed for these groups, yielding three groups of low, medium and high psychosocial load. See Table 5 for a summary of the findings.

Throughout the analyses, there was a positive relationship between factors of psychosocial stress and cortisol, i.e., the more burdened children had higher cortisol levels. Psychosocial stress was most consistently related to early morning cortisol, less so to evening cortisol and no difference was found for late morning (1030h) cortisol.

Paper II

The OCD group displayed the expected decrease in cortisol concentrations over the day (p < .001), and differed from the reference group in early morning cortisol levels (p = .005, M (SD) nmol/L: OCD = 8.3 (2.9), reference group= 5.7 (4.2)), while there was no cortisol difference in the late morning or in the evening (both ps > .10). The OCD group differed also in the cortisol response to an acute stressor (p < .001, percentage change M (SD): OCD = -10.0 (23.4), reference = 16.8 (52.8)). The change from baseline was near-significant in the OCD group (p = .076). No cross-sectional relation was found between cortisol and the clinical measures of symptoms severity (C-GAS, CGI, CY-BOCS), neither did cortisol predict the change in symptoms from intake to 6 months.

Thus, the children with OCD displayed higher morning cortisol and a lower response to acute stress than the reference group, while there was no relation between cortisol and clinical symptoms. See Table 5 for a summary.

Table 5. Summary of main results involving salivary cortisol measures (Paper I, II and III). Numbers are cortisol concentrations (nmol/L) if not noted otherwise. See the text for details. All p values are unadjusted for multiple comparisons.

Paper I	Number of psychosocial factors			Main results
Cortisol	0	1-2	3	1-2 and 3 vs 0 factors
sampling time	(n=156)	(n=109)	(n=8)	(M-W, Cohen's d^*)
0830h, <i>Md(IQR)</i>	4.4	5.3	4.8	
	(3.4-5.6)	(4.0-6.8)	(3.9-22.4)	1-2 > 0: $p < .001$; $d = .37$
1030h, <i>Md(IQR)</i>	3.2	3.2	3.6	
	(2.4-4.0)	(2.7-4.1)	(2.4-14.8)	ns
2100h, <i>Md(IQR)</i>	0.9	1.0	2.2	
	(0.6-1.3)	(0.6-1.5)	(1.2-10.3)	3 > 0: $p = .005$; $d = 1.1$

Paper II	Gro	oup	Main results
Cortisol	OCD	Reference	OCD vs Reference
sampling time	(n=22-23)	(n=240-336)	(t test, Cohen's d)
0830h, <i>M</i> (<i>SD</i>)	8.3 (2.9)	5.7 (4.2)	p = .005, d = .70
1030h, <i>M</i> (<i>SD</i>)	4.1 (1.8)	3.5 (2.2)	ns
2100h, <i>M</i> (<i>SD</i>)	1.0 (0.5)	1.3 (1.8)	ns
Response, $M(SD)$	-10.0 (23.4) %	16.8 (52.8) %	p < .001, d = .66

Paper III	Abused adolescents	Main results
Cortisol sampling time	(N=15)	Correlation to mental health measures (Pearson's <i>r</i> , Cohen's <i>d</i>)
0830h, <i>M</i> (<i>SD</i>)	10.2 (3.5)	p = .015030, r = .5661, d = 1.4 - 1.5
1030h, <i>M</i> (<i>SD</i>)	4.8 (2.4)	p = .016028, r = .5761, d = 1.4 - 1.5
2100h , M(SD)	1.3 (1.3)	ns

M-W = Mann-Whitney U test, Md = Median, IQR = Interquartile range, OCD = Obsessive-compulsive disorder

^{*} Calculated on log-transformed cortisol values.

Paper III

The cortisol AUC correlated significantly with internalizing symptoms (r = .56), with a tendency to correlate with externalizing symptoms (r = .48). Cortisol as measured at different times of the day revealed a pattern in the associations to the mental health measures: both early and late morning cortisol correlated significantly, and positively, with internalizing and externalizing symptoms (r = .56-.61, all ps < .05). Numerically, the correlations differed somewhat regarding post-traumatic symptoms (early morning, r = .30, p > .10; late morning, r = .59, p < .05) and sense of coherence (early morning , r = -.61, p < .05; late morning, r = -.042, p > .10), but the correlations were in the corresponding direction, i.e., positive for symptoms and negative for SOC. Evening cortisol concentrations, on the other hand, did not correlate with either symptoms or SOC (r = -.13-.19, all ps > .10).

Thus, the psychological measures correlated specifically with early and late morning cortisol, with no association to evening cortisol. Internalizing and externalizing symptoms were consistently and similarly related to cortisol, with post-traumatic symptoms and SOC somewhat less reliably so. Symptoms were consistently positively and SOC negatively related to cortisol. See Table 5.

Paper IV

In the final model (see Figure 3), when the other symptom dimension was controlled for, family social class and immigrant family were significantly related to emotional symptoms (ES) but not to conduct problems (CP); immigrant family also differed significantly between the ES and CP models (p < .05). The reverse was true for interpersonal traumatic events which were only related to conduct problems, but not to emotional symptoms; interpersonal differed near-significantly between ES and CP (p < .10). Interpersonal events were significantly more strongly related to CP than non-interpersonal events were (p < .01), while there was no difference for ES.

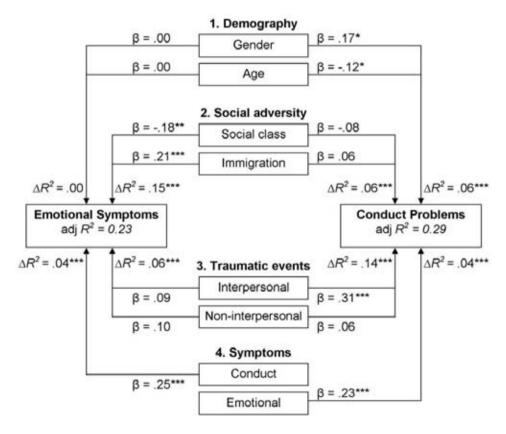


Figure 3. Summary of two separate hierarchical regression analyses in four steps, with emotional (internalizing) symptoms and conduct (externalizing) problems as dependent variables, respectively. Numbers are ΔR^2 for each set at entry, standardized regression coefficient (β) for each predictor in the final model, and adjusted R^2 for the final model. * p < .05, *** p < .01, *** p < .001

Paper V

Lifetime exposure to at least one traumatic event was found to be common, in both the samples of children (63%) and adolescents (89.5%).

In the younger sample, only 6 of the 15 events were significantly related to symptoms. The strength of these relations decreased somewhat when the occurrence of other events was taken into account, indicating a partial dependence on polytraumatization. In contrast, those events most clearly related to symptoms (been hit (item 11) and been threatened (item 14)) displayed even a stronger independent association than PT did. In the adolescent sample, 11 out of 15 events were significantly associated with symptoms, but the strength of the relationships diminished after consideration of PT, becoming non-significant for 6 of the events. As for the school-age sample, the events most strongly related to symptoms were the most independent of the PT addition (violence within the family (item 9), been hit (item 11), sexual abuse (item 13)). Of note is that in both samples, the events most independently associated with symptoms were all interpersonal events.

Regarding gender patterns in the impact of interpersonal and non-interpersonal events, IP events were consistently more strongly related to psychological symptoms than were nIP events. This was true for both boys and girls in both samples (all ps < .05), although there were some minor differences between the subgroups.

DISCUSSION

Summary of Findings

This thesis aimed at examining the relationships between different forms of psychosocial stress, mental health and cortisol as a marker for HPA axis activity, in children and adolescents, living under ordinary and adverse conditions.

As displayed in Paper I, adverse psychosocial factors appear to be related to higher activity of the HPA axis in children. Distal factors related to the broader social situation and more proximal factors linked to the functioning of the child in the immediate social environment combined in their association to cortisol.

Paper II indicates that children with OCD display higher HPA axis activity in the morning. Furthermore, this group of children showed a cortisol non-response – with a tendency to decreasing levels – to an acute psychological stressor.

Paper III points towards cortisol levels being related to mental health, in adolescents exposed to abuse. More trauma-related symptoms and less sense of coherence were related to a higher HPA activity in the earlier part of the day.

Paper IV demonstrates that social disadvantage and traumatic life events are related to both internalizing and externalizing symptoms in children. However, when taking the other symptoms dimension into account, social disadvantage only related to internalizing symptoms. In contrast, traumatic life events and particularly interpersonal traumas only related to externalizing symptoms

Paper V suggests an importance of cumulative traumas, polytraumatization, for the mental health of both school-aged children and adolescents. However, interpersonal events generally seem to impact more independently of other events, and more severely across gender and age groups, than non-interpersonal event.

Limitations

Design and Analysis

All studies in this thesis are cross-sectional, so the direction of causality cannot be confidently inferred on the basis of the results. Indeed, most of the studied constructs (psychosocial function and adjustment, cortisol, traumatic life events) have in longitudinal studies been shown to exert bidirectional influences on each other. This is a feature of linked systems, which one must bear in mind when drawing conclusions from the studies. Moreover, noncausal relationships involving unidentified third variables are also possible.

The school-age sample was a convenience sample, with consideration taken in the selection of schools. The aim was to get a total sample with a diverse representation regarding sociodemographic and neighborhood factors. The sociodemographics approximately corresponded to national statistics, with some overrepresentation of immigrant families. The SDQ scores matched those of the Swedish standardization (Smedje et al., 1999), suggesting a representative sample. There was, however, a higher general drop-out rate at the inner-city school, compared to the urban fringe school. This kind of selective participation is difficult to avoid, and the effective sample still included a high proportion of immigrant and low-SES families. Nevertheless, this should lead readers to employ some caution when generalizing the results.

The traumatized adolescents and OCD samples were both clinical convenience samples. Design issues related to the cortisol measures in the OCD sample are discussed below. The inferences drawn from Paper III are limited due to the correlational design and the small sample size. The small N confers large confidence intervals of the correlation coefficients, indicating that although they may differ from zero, these estimates are very uncertain. Likewise, the low power hampered statistical inference about several rather strong correlation coefficients, which remained statistically nonsignificant. The low n/k ratio did not allow for multiple regression analysis, limiting the likelihood to observe specific relationships between cortisol and psychological measures. Multiple testing was conducted without any correction. The results should be regarded with caution and are best viewed as exploratory.

In Paper I, the cortisol levels where positively skewed, with a few high values. The high values were consistent for these individuals over the sampling days and were not due to blood contamination, so were included in the analyses. However, this conferred a marked heteroscedasticity which, in combination with the unbalanced design, was deemed to be too influencing to conduct an ANOVA. Therefore, nonparametric alternatives were chosen as the main methods. An alternative analytical approach would have been ANOVA on log transformed cortisol concentrations.

Environmental Measures

There is a theoretical limitation in Paper I regarding the three psychosocial factors used. Two are sociodemographic variables, while one is teacher-rated impact of psychiatric problems on social function. These variables are obviously different in nature and operate at different levels. Still, they are all indicative of children at psychosocial risk. The study is unable to delineate any specific relationships, so the conclusions drawn should be general.

Regarding the retrospective reporting of traumatic events, methodological issues include general or selective underreporting, especially by parents on sensitive items such as domestic violence and sexual abuse. A general underreporting by parents is probable, considering the higher frequencies of traumas in the adolescent sample, even in children of similar age. Selective underreporting by parents on sensitive family items is difficult to evaluate based

on the data. The frequency of sexual abuse was of similar frequency in both samples, and the experience of domestic violence and being locked up were reported about twice as frequently in the adolescent sample. This frequency difference could be plausible given that the adolescents are considerable older and the results are of similar magnitude as several non-interpersonal items (e.g., car accident). Being beaten, threatened and robbed were all reported considerably more frequently in the adolescent sample. Since being robbed would not be expected to be selectively underreported by parents, the relatively higher frequency could perhaps, at least partially, be explained by juvenile violence. In any case, self-reported measures of trauma exposure may not be appropriate for 6-year-old children. These problems are, however, inherent in the checklist approach and should not be disregarded. In addition, the single use of parents (Paper IV and V) and youths (Paper V) may confer mono-informant bias, e.g. attempts to give meaning to problems may lead to over-reporting.

The distinction between interpersonal and non-interpersonal events may be confounded by other characteristics of these specific sets of traumatic events. Although both classes tap into physical injury and threats of physical injury and events that happened to oneself or to another person, there is greater portion of events directed at others of the nIP type. However, the bivariate results in Paper V do not suggest that this would be a major explanation. Still, the specific selection of events included in a life event checklist may influence the results significantly. The results have to be replicated using another, preferably more comprehensive, selection of potentially traumatic events.

Psychological Measures

The validity and reliability of the SDQ, TSCC and SOC are considered at least adequate. However, the reliance on parent-rated symptoms has some deficiencies. Parents may not be a optimal raters of children's internalizing symptoms (Achenbach, McConaughy, & Howell, 1987). The observed specificity of symptom dimensions in Paper IV could potentially be confounded by this, which could perhaps explain the generally lower explanation of emotional than conduct problems. Parent- and self-rated symptoms may, however, be better correlated in school-aged children than in adolescents (Achenbach et al., 1987).

In contrast to TSCC, SDQ is not a measure designed to tap into trauma-related symptoms. Indeed, the associations were weaker in the school-age than in the adolescent sample. This may represent a combined effect of the use of parents as raters (of both trauma exposure and symptoms), and the use of SDQ instead of a more trauma-focused questionnaire, such as Trauma Symptom Checklist for Young Children (TSCYC) (Briere et al., 2001). However, using a general screening questionnaire may be more appropriate when studying the relationship to socioeconomic factors.

Cortisol Measures

We had no control over to what degree the participants adhered to the sampling protocol at home. There is a possibility that the adherence could be a confounding factor, e.g., that the family conditions of the most burdened children in Paper I influenced the adherence. However, differences were primarily seen for morning cortisol levels, when sampling was done in the school under more controlled conditions.

The greater imprecision of the immunoassay method at lower concentrations affects the evening samples more than the other sample times, since concentrations were generally lower in the evening. In combination with a considerably larger portion of samples below the detection limit for the evening samples, the estimates regarding this time of the day would be expected to be less reliable. This could lead to type II error, and is a possible partial reason for the generally negative results concerning evening cortisol values.

After the data collection was completed, Salimetrics reported a high lot-to-lot variation (>15%) with the cotton rolls used for saliva collection in this thesis, and recommended switching to another type of cotton swab. This confers a potential problem of imprecision, but such preanalytical issues are included in the Total CV reported in the Methods section.

In Paper II, several differences between the samples could influence the results. First, the age differed between the samples. The relationship between age or puberty and cortisol in children is inconsistently reported in the literature (Groschl, Rauh, & Dorr, 2003; Knutsson et al., 1997; Rosmalen et al., 2005; O. P. Soldin, Hoffman, Waring, & Soldin, 2005; S. J. Soldin, Murthy, Agarwalla, Ojeifo, & Chea, 1999; Tornhage, 2002), although some studies have found small gender-dependent increases around puberty (Elmlinger, Kuhnel, & Ranke, 2002; Netherton et al., 2004). Second, the OCD subjects were all of subjective normal weight, while some children in the school sample were overweight or obese. Body mass has been shown to be related to cortisol in youth (Chalew, Lozano, Armour, Zadik, & Kowarski, 1991; Roemmich, Smith, Epstein, & Lambiase, 2007). Thus, age, gender and weight were potential confounders. Exploratory analyses with matched cases suggested that neither age, gender nor body mass explained the reported results.

Regarding basal cortisol levels, sampling was done at home on weekends for the OCD sample and on schooldays in the school sample. Cortisol levels may differ between weekdays and weekends for adults (Thorn, Hucklebridge, Evans, & Clow, 2006) and for children (Bruce, Davis, & Gunnar, 2002; Gutteling, de Weerth, & Buitelaar, 2005). However, since those results indicate elevated cortisol levels on weekdays, this would act to reduce the observed differences. There could also be differences in adherence to the sampling protocol, e.g., easier to forget the sampling times at home at weekends. This information was

not collected from the participants; self-reported compliance may not be a very good measure, anyway (Broderick, Arnold, Kudielka, & Kirschbaum, 2004). Moreover, studies on adults point towards noncompliance being associated with an underestimation, rather than an overestimation, of the cortisol response to awakening (Broderick et al., 2004; Kudielka, Broderick, & Kirschbaum, 2003). We did not synchronize the cortisol sampling to awakening time. Assuming the children woke up later on weekends than on weekdays, awakening time is a potential confounder.

The acute stress paradigms differed between the samples, and therefore the comparison of the responses may be of low validity. However, we would expect the exposure treatment to be more anxiety-provoking than a fire-alarm. In contrast, the cortisol responses differed between the samples in the opposite direction. Still, the possibility for the exposure treatment being a lower threat must be taken into consideration. Furthermore, the exposure treatment was known in advance, so the relative decline in cortisol levels in the OCD group could perhaps reflect a decline after a cortisol response to a distressing anticipation to the exposure treatment. Although anticipation is known to raise cortisol levels, previous studies on adults have indicated that exposure treatment, known in advance, is still capable of eliciting a cortisol response (Alpers, Abelson, Wilhelm, & Roth, 2003; Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; Garcia-Leal et al., 2005), suggesting that masking of the cortisol response would not be an issue. Furthermore, there were no differences between prestress cortisol levels in the OCD group, and either late morning levels in the OCD group or pre-stress levels in the reference group, suggesting that anticipation did not influence the results majorly. In future studies, such issues should be controlled by using a design with higher constraints.

Interpretations of Findings

Psychosocial Stress and Cortisol

The results of Paper I are in concordance with the findings of others, with higher cortisol in children of low SES (Kapuku, Treiber, & Davis, 2002; Lupien et al., 2000, 2001) or in poverty (Evans & English, 2002; Evans & Kim, 2007). The children with a moderate degree of psychosocial load displayed higher morning cortisol. Interestingly though, the cortisol pattern in the most exposed group of children is indicative of a flattening of the diurnal rhythm. This is a pattern of the HPA axis previously observed in children of ethnic minority (DeSantis et al., 2007) or reared in orphanage (Gunnar & Vazquez, 2001). Furthermore, in one study, school children exposed to both recent and previous traumatic events displayed a flattening of the cortisol rhythm (lower morning and higher evening cortisol), while those only exposed to recent traumas demonstrated only higher morning cortisol (Bevans et al., 2008). A flattened cortisol rhythm has in animal

models been shown to impair hippocampal function (Gartside, Leitch, McQuade, & Swarbrick, 2003; Leitch, Ingram, Young, McQuade, & Gartside, 2003), indicating that this pattern has adverse neurobiological consequences. A tentative interpretation could be that a moderate degree of psychosocial burden may confer a pattern of dysregulation – here mainly higher morning values – while a pervasive burden may have a greater tendency to result in another pattern – flattening of the diurnal rhythm. The cumulative effect could also represent previous insults conferring a psychobiological vulnerability to later stress exposure. However, considering the small subsample size (n = 8) this finding should be viewed with caution.

The possible explanations of the findings are numerous but speculative. Low SES and ethnic minority of the parents may affect the stress exposure of children in a multitude of possible ways; through family systemic stress due to economic hardship, insecure job conditions, through other microsystems due to insecurity and violence in neighborhood and school (Attar et al., 1994; H. A. Turner, Finkelhor, & Ormrod, 2007), as well as direct interaction with the macrosocial system due to inequality (Sapolsky, 2005; Wilkinson, 1999). Impairment in social functioning due to psychiatric problems is another factor that was measured, and which potentially can activate the HPA axis because of strained social relationships in microsystems, e.g., the peer and school contexts.

The observed disturbance of the HPA axis in psychosocially burdened children may represent allostatic load, which over time could lead to adverse health consequences. This may be one pathway along which social conditions in childhood confer worse health in adulthood (Guralnik, Butterworth, Wadsworth, & Kuh, 2006; Moody-Ayers, Lindquist, Sen, & Covinsky, 2007). Although the results do not demonstrate later health risks, they are consistent with the idea that stress systems may play a role. Furthermore, the results display that this is a possible pathway even in a society with well-developed welfare systems.

One or more psychosocial factors were actually enough to create a discernable difference in cortisol levels. Considering that 40% of the children had at least one of these factors, this is certainly interesting. One could argue that the high frequency, together with the rather small cortisol differences between the groups, would suggest that these differences may not be connected to any health consequences.

However, I would argue against disregarding the findings so easily. First, it has been shown that childhood SES confers long-term effects on the cortisol secretion (L. Li, Power, Kelly, Kirschbaum, & Hertzman, 2007) and health (Lipowicz, Koziel, Hulanicka, & Kowalisko, 2007; Melchior, Moffitt, Milne, Poulton, & Caspi, 2007) into adulthood, independent of SES in adulthood. Second, it is also clear that the risk for ill health varies over the whole SES spectrum; implicating that the increased risk is not limited to the most unprivileged (Adler et al., 1994). Third, small differences are expected. In our study we measured a single component of a single biological system; cortisol is

but a small piece in a huge jigsaw puzzle of multiple physiological systems. Fourth, even small differences can potentially result in wide nonlinear consequences, considering the multitude of interacting systems.

The psychobiological impact of social conditions may in the future present an additional argument for improving the life situation of disadvantaged children. Such improvements are preferably done through preventive efforts. Examples of proposed harmful aspects of social disadvantage are poor family economy (Conger et al., 1994), neighborhood disadvantage (Aneshensel & Sucoff, 1996; Kalff et al., 2001) and relative inequality (Pickett & Wilkinson, 2007). Prevention, based on political rather than medical methods, could therefore be directed at improving the economic situation of low-income families, diminishing social segregation and moving towards a more egalitarian society.

Elevated Morning Cortisol

All studies reported in the three papers examining cortisol observed positive results regarding early morning cortisol, while the results for late morning and evening cortisol were inconsistent. Taken together, these three studies point towards numerical outcome specificity on early morning cortisol, by psychosocial stress (Paper I), OCD diagnosis (Paper II) and trauma-related symptoms (Paper III). Morning cortisol was also elevated in all studies, i.e., a positive relationship between cortisol and the psychosocial and psychiatric conditions. Thus, if not explained by methodological issues, HPA axis hyperactivity in the morning seems to be an example of equifinality in these studies of diverse conditions of stress in childhood.

Elevated morning cortisol, as opposed to evening cortisol, has also been found to be predictive of the onset of pediatric depression in a high-risk sample (Goodyer, Herbert, Tamplin, & Altham, 2000), as well as mediating the association between maternal postnatal depression, and the risk for depression in adolescent offspring (Halligan, Herbert, Goodyer, & Murray, 2007; Halligan, Herbert, Goodyer, & Murray, 2004). This indicates a preferential impact of psychosocial stress on the earlier part of the diurnal HPA rhythm, as well as an importance of this cortisol pattern for child development. It is also a good example of how disturbances in the mental subsystem of the mother (postnatal depression), resound in the family system and mother child subsystem, in the biological system of the child (cortisol hypersecretion) and in the mental subsystem of the child (depression). Specificity for morning cortisol has, as mentioned below, also been shown in several studies of trauma in child or adolescent samples, notably including the impressive papers by Cicchetti & Rogosch (2001a; 2001b; 2007). The psychobiological literature on children and adolescents is however far from consistent in this regard (Pervanidou et al., 2007).

Although singularly elevated morning cortisol levels were not a consistent finding in this thesis, a speculative examination of this finding may be warranted. Then, what could the reason be for an impact on a specific part of the diurnal rhythm? A possible explanation is that early morning cortisol is related to the cortisol peak in the morning, the cortisol awakening response (CAR). CAR has, however, been shown to actually be a response to awakening, superimposed on and rather distinct from the diurnal rhythm (Hucklebridge, Hussain, Evans, & Clow, 2005; Wilhelm et al., 2007), and not related to the acute response to psychological stress (Schmidt-Reinwald et al., 1999). CAR has been shown to be related to various stress-related circumstances or conditions in adults (Clow, Thorn, Evans, & Hucklebridge, 2004), and increased in adolescents at psychosocial risk (Ellenbogen, Hodgins, Walker, Couture, & Adam, 2006). Although we did not measure CAR per se, the early morning cortisol concentrations could, perhaps, reflect a rough approximation of CAR, in that the processes influencing the morning cortisol levels may be partly different from those during the later part of the day. Indeed, early morning cortisol concentrations have been shown to be unrelated to the diurnal secretion, in contrast to cortisol levels later in the day (Edwards et al., 2001). Cortisol levels also seems to be elevated at least 60 minutes after awakening (Clow et al., 2004). In the school children sample of Paper I and II, we also found lower correlations of late morning (1030h), and early morning (0830h, r = .19), than to evening (2100h, r = .40), contrary to what the time-intervals would suggest. Thus, although somewhat sketchy, the early morning cortisol levels could be viewed as a rough approximation of the CAR, at least for this discussion.

Although influenced by the circadian rhythm, CAR is thought to mostly reflect processes related to the sleep-wake transition (Wilhelm et al., 2007). Awakening is marked by a general cortical arousal, initiated by projections from the midbrain reticular formation, to thalamus and cortex (Akerstedt et al., 2002). CAR has been proposed to depend on spontaneous retrieval of memory representations, such as those related to self-concept and life conditions (Wilhelm et al., 2007). This is supported by the studies finding that CAR is abolished in patients with global amnesia (Wolf, Fujiwara, Luwinski, Kirschbaum, & Markowitsch, 2005), and in patients with hippocampal damage (Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004), despite normal cortisol rhythm during the rest of the day. Intact memory and hippocampal function may be necessary to know what to expect of the coming day, and this hippocampusdependent memory retrieval elicits a physiological response (Buchanan et al., 2004). As Wilhelm et al. (2007) suggest, the retrieval of traumatic memories or the apprehension of a demanding life situation could, perhaps, explain CARs association to stress-related conditions. This could also be an explanation why, in the present thesis, a preferential importance of morning cortisol was found. However, another aspect of relevance is that morning cortisol levels seem to be genetically influenced to a greater degree than evening levels in children

(Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003). This stands somewhat at odds with the suggestion that morning cortisol would be more susceptible for environmental influences in children than evening cortisol levels.

The health consequences of an accentuated cortisol morning peak in childhood are unclear. Elevated morning cortisol may, however, signify a form of development-dependent HPA dysregulation in burdened children and adolescents. Possibly, this may confer physiological vulnerabilities for future stress exposure and health risks, as a representation of allostatic load. Future research will hopefully elucidate both the developmental issues and the consequences of these dysregulations.

Trauma and Cortisol

The result of Paper III are in accordance with several studies on traumatized youths, where cortisol relate to trauma exposure or symptoms thereof (Carrion et al., 2002; Cicchetti & Rogosch, 2001a, 2001b; De Bellis et al., 1999; Gunnar et al., 2001; Murali & Chen, 2005; Pfeffer et al., 2007; Saltzman et al., 2005).

There are several important methodological differences between these previous studies, which limits the conclusions that can be drawn. Factors that may be important are the general study design, diversity within trauma-exposed groups (Yehuda, 2006), method of HPA axis measurement (resting conditions or challenge), sample definition (by trauma, PTSD diagnosis or both) (Bremner, Vermetten, & Kelley, 2007; Young & Breslau, 2004), comorbidity (Yehuda, Halligan, Golier, Grossman, & Bierer, 2004), trauma characteristics (Cicchetti & Rogosch, 2001a) and duration and timing of trauma (Gunnar et al., 2001).

However, even the tendency for a positive relationship between trauma and cortisol in children is interesting, since it contradicts some findings in adult samples. In several studies, lower cortisol levels have been found in adults exposed to trauma or with higher levels of trauma-related symptoms (Luecken, Dausch, Gulla, Hong, & Compas, 2004; Neylan et al., 2005; Pico-Alfonso, Garcia-Linares, Celda-Navarro, Herbert, & Martinez, 2004; Wessa, Rohleder, Kirschbaum, & Flor, 2006; Yehuda, Golier, & Kaufman, 2005; Young & Breslau, 2004). This pattern of cortisol secretion was first thought to be typical for adult PTSD (Heim et al., 2000; Yehuda, 1998), but that view has been revised to some degree, since there are many inconsistent findings in the literature (Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007; Yehuda, 2006).

Nevertheless, the differencies between the cortisol levels in adults and children are interesting. Considering that the trauma types studied in adults are often not the same as those studied in children, two examples from more homogenous trauma types will be discussed to evaluate this possibility.

First, as presented in a recent meta-analysis, hypocortisolism seems to be more prevalent in subgroups of adult PTSD patients: in those exposed to trauma a long time ago (>20 years), in sexually/physically abused (as opposed to e.g.,

military combat), and in females (Meewisse et al., 2007). All these features match a history of childhood abuse. Indeed, hypocortisolism has repeatedly been observed in adult survivors of childhood abuse (with or without PTSD), or related to symptoms of childhood abuse, also in studies not included in the mentioned meta-analysis (Bremner et al., 2007; Brewer-Smyth & Burgess, 2008; Brewer-Smyth, Burgess, & Shults, 2004; Yehuda, Halligan, & Grossman, 2001). These studies indicate that exposure to interpersonal traumas in childhood is connected to lower cortisol levels in adulthood, contrary to the hypercortisolism found in traumatized young people.

Second, another indication is a series of studies by the same research group, regarding acute non-interpersonal trauma in the form of severe accidents. In these studies, cortisol levels in the direct aftermath of trauma were examined as a predictor of the later development of posttraumatic symptoms (PTSS). In children, cortisol levels were found to predict PTSS positively (Delahanty et al., 2005; Nugent et al., 2006; Ostrowski et al., 2007), which is consistent with a positive relationship between cortisol and symptoms in child trauma victims. This is also consistent with the findings of others (Pervanidou et al., 2007). In contrast to this, in mothers of child trauma victims, lower cortisol predicted PTSS (Ostrowski et al., 2007). Similarly, in a separate study of adult vehicle accident victims, lower peritraumatic cortisol predicted the development of PTSD (Delahanty, Raimonde, & Spoonster, 2000). These results from studies – with similar design – provide further evidence for an age-dependent association between trauma exposure and the HPA axis.

The difference between the results for children and adults has been noted by others. The initially high cortisol in traumatized children has been proposed to be an early pattern eventually developing into a "mature" state of hypocortisolism, including increased cortisol feedback, in vulnerable individuals (De Bellis et al., 1999; Pervanidou, 2008). One explanation is that previous trauma exposure is a vulnerability factor for the low cortisol profile more often seen in adults, and that children, in general, have experienced fewer traumatic experiences due to their younger age (Delahanty & Nugent, 2006; Pervanidou, 2008). This is supported by findings of the impact of time since trauma in clinical (Weems & Carrion, 2007) and non-clinical (Bevans et al., 2008) samples of children, but contradicted by some results (M. J. Friedman, Jalowiec, McHugo, Wang, & McDonagh, 2007). The other explanation is that children respond differently than adults do, owing to an immature stress system, and that the divergent findings thus is an expression of a development-dependent pattern (De Bellis et al., 1999). This is supported by findings of hypocortisolism in adult survivors of childhood abuse more often than in other forms of traumatizations (Meewisse et al., 2007).

Thus, the findings of Paper III corroborate the hypothesis of a positive relationship between cortisol levels and aspects of trauma in young subjects. The results may stand for at least three theoretically possible, causally distinct but not mutually exclusive, relationships. First, HPA activity may be a result of perseverative mental distress, represented by psychiatric symptoms and low SOC. Second, the severity of traumatization might produce degrees of long-lasting cortisol hyperactivity, which in turn might influence trauma-related symptomatology, e.g., through cortisols effect on limbic structures. Third, the severity of trauma might influence both mental sequalae, and a long-term HPA axis sensitization, conferring a psychobiological imprint parallel to the mental health consequences. Most likely the cortisol hypersecretion represents a central HPA axis hyperactivity, with increased CRH secretion in the most severely affected adolescents. Later in life, possibly after the accumulation of additional insults, the chronic hypersecretion of cortisol may develop into increased cortisol feedback at the pituitary, resulting in a relative hypocortisolism (Yehuda, 2006).

The observed dysregulations could potentially be of pathophysiological relevance for the mental health of traumatized adolescents (Goodyer, Park, Netherton, & Herbert, 2001; McAllister-Williams et al., 1998; Penza et al., 2003). Moreover, considering the wide range of physical health risks childhood abuse confer during the life course (Chartier, Walker, & Naimark, 2007; Felitti et al., 1998; Springer, Sheridan, Kuo, & Carnes, 2007), biological stress systems may also play a role in the development of physical disease. The HPA axis dysregulations could thus signify allostatic load, acting as a chronic biological stressor to other bodily systems with possibly long-term consequences.

Child maltreatment represents a failure of society to take care of children, and clearly leads to substantial consequences for the individuals, families, and for society at large (Harris, Lieberman, & Marans, 2007). The ideal way to respond to this is through the development of primary preventive strategies (Klevens & Whitaker, 2007), e.g., by creation of programs directed at high-risk families (Geeraert, Van den Noortgate, Grietens, & Onghena, 2004). The indication of an effect on biological stress systems may seem to be of secondary importance when the impact of maltreatment is addressed. However, these findings document a pervasive impact on the whole individual and indicate that future health risks may not only depend on other factors, such as risk behavior, but also on the direct effect on physiological systems. The reversibility of HPA axis dysregulations following successful treatment in young people is a major issue to be studied in future research. If HPA axis dysregulation are shown to be resistant to treatment, then this would be an additional argument for primary prevention in preference to treatment of sequelae. If, on the other hand, dysregulations are shown to be reversible, this would in addition emphasize the importance of successful identification and care of traumatized children and adolescents.

The role of the HPA axis in mood and anxiety disorders may also offer a target for pharmacological treatment. Although the clinical evidence to date is meager, preliminary results in adults of glucocorticoid antagonists in mood

disorders (Gallagher et al., 2008), glucocorticoid agonists in PTSD (de Quervain, 2008) and CRH1-receptor antagonists in mood and anxiety disorders (Holsboer & Ising, 2008) are promising. This may in the future lead to new treatment options that could benefit children and adolescent. However, the mounting evidence of different HPA axis patterns in traumatized younger subjects compared to adults must be taken into consideration. These age-dependent psychobiological differences in traumatized subjects emphasize that it is ill-advised to extrapolate results from adults to children. Future studies should aim at examining the influence of development in more detail, taking into account time elapsed since the trauma, and the effect of previous trauma history, on the psychobiological consequences of trauma, preferably by longitudinal design.

Lastly, there may be a theoretical point in stressing the biopsychosocial unity of the human being, which is the position indicated by Paper III, instead of a mind-body dichotomy. This may yield a more holistic view on the human being and stimulate future integrative research.

Obsessive-Compulsive Disorder and Cortisol

Although no comparable studies have been conducted on young OCD subjects, basal cortisol hypersecretion is in concordance with what have been found in adults with OCD (Catapano et al., 1992; Kluge et al., 2006; Monteleone et al., 1994; Monteleone et al., 1998; Monteleone et al., 1995).

Cortisol levels were not predictive of symptoms at intake or 6 months later. This result does not support a predictive, potentially pathophysiological, role of the HPA axis in the longitudinal progress of OCD, contrary to what has been found in pediatric depression (Goodyer et al., 2000; Halligan et al., 2007).

It is interesting that a smaller pituitary volume, negatively related to symptoms, has been found in children with OCD (MacMaster, Russell, Mirza, Keshavan, Banerjee et al., 2006). Tentatively assuming that these findings reflect a hyposecretion of ACTH, the results would be consistent with cortisol hypersecretion if there was an increased adrenal sensitivity for ACTH, as well as either 1) increased pituitary and/or hypothalamic sensitivity for cortisol feedback (inhibiting ACTH secretion), or 2) a CRH hyposensitivity/habituation of the pituitary (resulting in low ACTH secretion despite high/normal CRH levels). Pituitary habituation to CRH, as a consequence of cortisol hypersecretion, has been observed in depression (Parker, Schatzberg, & Lyons, 2003). However, the studies are obviously too few for any firm conclusions to be drawn, and a plea for more research on the subject is therefore suitable.

Cerebrospinal fluid (CSF) CRH has been measured in two studies on pediatric OCD patients. While no relation to symptom severity was found in one (Swedo et al., 1992), a reduction following treatment was found in the other (Altemus et al., 1994). The value of these results for HPA axis physiology is doubtful

though, since CRH functions as a neurotransmitter in several brain regions outside the HPA axis (Claes, 2004). Based on the lack of correspondence between CSF CRH concentrations and ACTH and cortisol levels, CSF CRH are thought to reflect mainly extrahypothalamic CRH (Baker et al., 1999; Geracioti, Loosen, & Orth, 1997).

The tendency to a decrease in cortisol in face of an anxiogenic exposure is initially surprising and paradoxical. The finding is also difficult to explain due to the lack of studies on children. Exposure treatment in adult phobic patients has been shown to be capable of eliciting a clear, positive, cortisol response that is greater than that of controls (Alpers et al., 2003; Condren et al., 2002). However, the literature is inconsistent, as a cortisol nonresponse also has been described in adult anxiety disorder patients, both in response to panic attacks (Cameron, Lee, Curtis, & McCann, 1987; Woods, Charney, McPherson, Gradman, & Heninger, 1987) and to pharmacologically induced anxiety (Abelson, Khan, Liberzon, & Young, 2007). A dichotomous response pattern has also been observed in a group of social phobic patients, where the majority of patients (n = 11/18) displayed a decrease in cortisol in response to a speech task (Furlan et al., 2001). These results show that a negative response is possible in anxiety disorder patients. A blunted cortisol response to psychological stress has also been observed in healthy adults exposed to adverse childhood experiences (Carpenter et al., 2007; Elzinga et al., 2008), despite normal sympathetic and subjective responses (Elzinga et al., 2008). A diminished acute cortisol response has also been seen in healthy subjects with high trait anxiety (Duncko, Makatsori, Fickova, Selko, & Jezova, 2006; Hubert & de Jong-Meyer, 1992).

The indicated HPA axis dysregulations in young OCD subjects in Paper II could depend on several causes, all speculative. First, it could reflect a higher level of nonspecific distress compared to healthy peers. Although we did not measure either subjective stress experience or objective stressor exposure, it certainly appears to be a valid interpretation, considering the repeated anxiety in OCD. For example, it is in accordance with one study showing increased daily stress experiences of both children with OCD and their parents (Lin et al., 2007). Daily fluctuations of worries and frustrations have been shown to influence momentary cortisol levels in youths (Adam, 2006). Interestingly though, we did not find any relationship between cortisol and symptom severity. According to the distress/stressor exposure explanation, higher levels of anxiety would supposedly lead to cortisol hypersecretion. The non-response to the exposure treatment could also depend on repeated exposure, or fear of exposure, since the HPA response to psychological stress is known to habituate with repeated exposure (to a larger degree than the sympathetic system) (Schommer, Hellhammer, & Kirschbaum, 2003).

Another possible explanation is dysregulations of the HPA activity as secondary to neurobiological features of OCD. Deficits in the limbic system

structures such as hippocampus, amygdala and prefrontal cortex, or regions highly connected to them, have been implicated in OCD pathophysiology (Friedlander & Desrocher, 2006). These structures are both important regulators of the HPA axis (Herman et al., 2003) and targets for cortisol action (McEwen, 2007). Abnormalities in the serotonin neurotransmitter system is a dominant neurochemical model of OCD (Stein, 2002). A hyposensitivity of the HPA axis to serotonin agonists has also been observed in adult OCD patients (Khanna et al., 2001; Lucey et al., 1992; Meltzer et al., 1997; Sallee et al., 1998), possibly reversible by successful SSRI treatment (Meltzer et al., 1997). This may indicate a defective serotonin-HPA link in OCD, as has been pointed out by some authors (Khanna et al., 2001). The serotonin system, projecting indirectly to the PVN mainly from neurons of the raphe nuclei, is an important complex modulator of the HPA axis (Chaouloff, 1993; Herman et al., 2003; Lowry, 2002), and is in turn influenced by glucocorticoids (Chaouloff, 2000). The serotonin system also plays a role in the prenatal and early life programming of the HPA axis resulting from stress exposure, and both systems are interacting during early life and reciprocally influence the development of each other (Andrews & Matthews, 2004). The mutual interdependence of these two systems has also been proposed as a pathophysiological theme in depression (Porter et al., 2004). Perhaps the HPA axis findings in Paper II therefore represent the co-development of the serotonin and HPA systems as a trajectory specific for OCD, and possibly a trait marker of the disorder.

Taken together, it is unclear what the suggested HPA dysregulations in Paper II signify. Still, if replicated in future research, it may represent the biological echo of the stressful lives of children with OCD, and there is a possibility that this may indicate future health risks. Although not a major line of current thought in OCD pathophysiology, the possibility of HPA-axis and serotonin joint defects in OCD may be a clinically relevant issue in future research. As an example, antiglucocorticoid therapy has been suggested in a case report as a successful adjunctive therapy for SSRI-resistant adult OCD (Chouinard, Belanger, Beauclair, Sultan, & Murphy, 1996), although this finding has not been pursued further.

Psychosocial Stress and Mental Health

Polytraumatization

The results of Paper V are generally consistent with previous results by Finkelhor and co-workers, regarding the impact of cumulative trauma, for which they have coined the term polyvictimization (Finkelhor et al., 2007a, 2007b). Paper V reports results that deal with a broader range of trauma types than Finkelhor studied, specifically by including non-interpersonal traumas.

The explanation for the negative influence of multiple different traumas may be that more people and environments in the life of a child are associated with traumatic reminders that hamper successful coping, and that above a threshold the defensive coping may become generalized to include most interpersonal contexts (Finkelhor et al., 2007a). The child may also to an increased degree react through negative self-attribution when the traumatization stems from multiple sources, and realization of deviance compared to peers may be more evident to the child (Finkelhor et al., 2007a). Multiple traumatization might also be a marker for increased psychosocial risk, e.g. owing to poor supervision.

The high frequency in combination with the impact of trauma in these school-based samples could stimulate the use of a simple screening instrument in child and adolescent mental health care. This may be useful for identifying children and adolescents who have been exposed to trauma; information that may be meaningful in the clinical situation even if it was not the focus at the time of the first contact. Furthermore, in the planning of treatment for traumatized children and adolescents, the importance of cumulative trauma may warrant a comprehensive probing of traumatic experiences other than the index trauma. This may give a better picture of the total traumatic burden of the youth, and may aid in identifying certain highly traumatized individuals.

Interpersonal traumas

The pervasive and independent impact of interpersonal traumas on symptoms, in both school-aged children and adolescents, and in both boys and girls, were displayed in Papers IV and V. The severe impact of interpersonal traumas has, as outlined in the introduction, been noted in the literature (American Psychiatric Association, 1994; Charuvastra & Cloitre, 2008; Norris, Friedman, Watson et al., 2002). We also found an indication that the effect may differ somewhat by gender. This may indicate different vulnerabilities (Nolen-Hoeksema & Girgus, 1994) or the type of symptom expressed (Achenbach et al., 1987), or might, on the other hand, just reflect the limitations of the measures.

Green (1990) proposed that the central aspect which explains the impact of interpersonal events is the matter of deliberateness or intentionality. The intentionality may bear important psychological characteristics, since the betrayal by another human being must be coped with in addition to coping with

the perceived threat. Similar explanations have been mentioned by others; difficulty in comprehending or assimilating actions guided by malicious human intent (Norris, Friedman, & Watson, 2002); or the struggle to assign human accountability, in the case of children witnessing domestic violence (Kilpatrick & Williams, 1997).

Interpersonal relationships are indeed key features in human development, and may have served the same purpose during evolution, whereby we have evolved to be dependent on social relationships (Cacioppo, Berntson, Sheridan, & McClintock, 2000; Reis, Collins, & Berscheid, 2000). The impact of interpersonal trauma may thus ultimately be a reflection of the evolutionary significance of social bonds, based on trust and mutuality, and the sense of threat and fear when these bonds are disrupted (Charuvastra & Cloitre, 2008). As a personal reflection, this notion is to some extent analogous to the health consequences of social hierarchy and inequality (Pickett & Wilkinson, 2007; Wilkinson & Pickett, 2006), which also represents forms of social relationships based on dominance rather than mutuality. Perhaps the convergence of these two lines of thought signifies the same social aspect of human nature.

The specific relevance of the impact of interpersonal traumas on children and adolescents can be viewed from two perspectives. On the one hand, it tells us something about what in the environment that is particularly harmful for children. Although there already is a clinical presumption of the severity of interpersonal traumas, awareness of the social dimension of trauma may be helpful in clinical practice. One the other hand, it tells us something about the importance of positive social relationships for the child and for the human being. Understanding of the atypical can aid our understanding of the normal, and vice versa.

Specificity of psychosocial stress

There are results that point towards outcome specificity of more harsh interpersonal circumstances in favor of externalizing problems in children and adolescents, such as harsh or inconsistent discipline by the parents (Dodge, Pettit, & Bates, 1994; A. Goodman, Fleitlich-Bilyk, Patel, & Goodman, 2007; Lempers, Clark-Lempers, & Simons, 1989). Similarly, conduct disorder has been found to be more strongly related to non-physical punishment and unhealthy family functioning than to income, as compared to emotional disorder (Vostanis et al., 2006). A history of violence exposure is more consistently related to externalizing than to internalizing problems in preschoolers (Jaffee, Moffitt, Caspi, Taylor, & Arseneault, 2002), school-aged children (Attar et al., 1994; Sternberg et al., 1993) and adolescents (SchwabStone et al., 1995). Moreover, physical childhood abuse and negect are related to an increased risk of violent behavior in adulthood (Maxfield & Widom, 1996;

Widom, 1989), partly mediated by early behavioral problems (Widom, Schuck, & White, 2006).

The development of externalizing behavior in the face of a threatening immediate environment could be explained by the effects of violence on social information processing. The effects of early exposure to violence on later aggressive behavior have been shown to be mediated by hostile attributional bias towards others (Dodge, Bates, & Pettit, 1990; Dodge et al., 1994). More specifically, this cycle of violence can be understood from a pathologic adaption perspective, as has been hypothesized regarding violence exposure in children and adolescents (Ng-Mak, Salzinger, Feldman, & Stueve, 2002). According to this model, exposure to violence may lead to cognitive normalization of violence, e.g., by moral disengagement. This psychological adaption serves as a buffer to emotional distress, but at the same time it increases the propensity for aggressive behavior. Hostile attribution, with externalizing behavior, can also be an adaptive strategy in a truly hostile environment, protecting the individual from self-blame and internalizing problems (Lansford et al., 2006). Thus, the relative outcome specificity of interpersonal events in favor of externalizing over internalizing symptoms may represent a form of adaptation to harsh interpersonal experiences.

Our results are also consistent with findings in some studies, where socioeconomic conditions are more strongly related to internalizing than to externalizing symptoms, independently of the proximal social environment (Atzaba-Poria et al., 2004; Grant et al., 2004; Lempers et al., 1989). This tendency of a relative preference for sociocultural factors over traumatic events for internalizing symptoms might be explained by the distant nature of the factors, the macrosystem, where the child itself is not an actor (Atzaba-Poria et al., 2004). These chronic insults may lead to feelings of helplessness and a tendency to attribute the distress to oneself (Lempers et al., 1989). Also, feelings of lack of safety and mistrust in neighborhoods are also more strongly related to children's internalizing than externalizing problems (Meltzer, Vostanis, Goodman, & Ford, 2007). This may also represent the constant worries of living in disadvantageous areas, with no apparent source to act out on. While socioeconomic factors indeed are related to externalizing problems, it may to a greater degree be explained by the association of SES and direct interpersonal circumstances (Lempers et al., 1989).

The literature on what environmental characteristics are related to what outcome in young people is extensive, but it is fundamental to child and adolescent psychiatry. It should be emphasized that emotional and behavioral problems are interrelated and not mutually exclusive, which also holds true for socioeconomic disadvantage and violence exposure. Due to this, stressor-outcome specificity would be expected to be relative and modest, rather than absolute and clear-cut. The findings of this thesis are at best minor contributions to this field, given the methodological issues.

MAIN CONCLUSIONS

The main conclusions of this thesis are:

- School-aged children in adverse psychosocial circumstances display higher cortisol levels.
- Children with OCD seem to display a high morning cortisol peak, and a cortisol non-response to psychological stress.
- Cortisol levels in the earlier part of the day are positively related to trauma-related symptoms, and negatively to sense of coherence, in adolescent who have been exposed to childhood abuse. This may be a different pattern than seen in adults exposed to trauma.
- Traumatic events with an interpersonal component are more strongly related to general mental health than non-interpersonal events, in both school-aged children and adolescents and in both boys and girls.
- Sociocultural conditions seem to be related to mainly internalizing symptoms, while interpersonal traumatic events seem to be mainly related to externalizing problems, in school-aged children.
- Cumulative traumatic event exposure, polytraumatization, appear to be more strongly related to the mental health of children and adolescents, than the single occurrence of most specific events are.

EPILOGUE

As indicated in Papers I and IV, the accumulated burden stemming from the broader social context relates to disturbances in mental and biological individual subsystems. This may indicate that a disadvantaged societal position acts as a stressor to the child through interfaces of the proximal environment such as the family system, the parent-child subsystem, and thus reverberating in the biological systems of the child. The additional burden of interpersonal traumatic experiences, as depicted in Papers III, IV and V, represents severely disturbed individual-social system interfaces. This may influence the child pervasively, affecting multiple subsystems such as the mental and physiological subsystems. The link between biological and mental subsystems is evident in the cortisolmental health relationships displayed in Paper III. Considering the reciprocal influences of HPA axis and the neurobiological subsystem, this may represent a bidirectional influence. The psychological development of externalizing behavior in face of interpersonal threats may be seen a homeostatic adaptation, but may bring about effects on adjacent social systems.

The disturbance in the HPA axis could affect other biological systems and through allostatic load constitute a stressor for the body. This could confer a developmental risk for physical disease. Another manifestation of the multiple system co-development may be OCD. Here, adverse development would include the mutually dependent serotonin and HPA systems, potentially leading to longterm dysregulations, programming, in both systems. These early environmentally and genetically influenced alterations could serve vulnerability for later insults. During later life, individual and family systemic stress could perhaps influence the onset and severity of OCD, through impacting on these neurochemical systems where cortisol modulate the serotonin output, and serotonin the HPA output.

The diverse facets of the lives of children can be viewed as working as a biopsychosocial whole. Consequently, to yield an understanding of any of these processes, the whole must be considered. The ultimate aim is to improve the well-being and health of children, and knowledge about the interactive processes influencing these outcomes is fundamental for creating supportive contexts for children, in their immediate surroundings and in society at large.

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