1.1 INTRODUCTION

> ***"Mental health — neglected for far too long — is crucial to the overall well-being of individuals, societies and countries and must be universally regarded in a new light."***
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> Dr. Gro Harlem Brundtland,
> Past Director-General World Health Organization (2001)

Why is it that some people become ill — physically and/or mentally — when others stay healthy? How can we find new ways to promote the health of individuals and societies? These are some of the important questions facing us today. To begin to answer them, we should attempt to unravel "predisease pathways" (Singer & Ryff, 2001). It is not sufficient to understand only the processes of illnesses or disorders once people are suffering from them; we need instead to identify very early developments that lead to illnesses, disorders, or disabilities, as well as those that lead to good health. For over 100 years, scientists have tried to understand the long-term effects of early adverse experiences, such as sexual or physical violence, emotional neglect, loss of parents or other important persons, catastrophes, and so forth. Indeed, epidemiological and case-control studies have shown that early adversities increase the risk for a great variety of mental disorders and physical illnesses (see Chapter 2 for details). For example, adverse childhood experiences (ACEs) in the form of genital childhood sexual abuse, especially intercourse, increase the risk for nearly all types of psychiatric disorders (most odds ratios exceed 3.0) (Kendler et al., 2000). Together with the relatively high prevalence of other forms of ACEs, this leads to the situation that a substantial number of individuals seeking therapy have suffered from ACEs. For example, in a multi-center study on chronic depression, nearly two-thirds of the subjects had experienced sexual or physical abuse, neglect, or parental loss during childhood (Nemeroff et al., 2003). Moreover, it has been shown that 70% of psychiatric outpatients report an abusive experience in childhood or adulthood (Lipschitz et al., 1996). This highlights the importance of understanding the consequences of early adversities if we want to know how and why people get ill or stay healthy.

The examination of the effects of early adversities began quite a while ago. At the beginning of the 20th century, Sigmund Freud made the important observation that early adverse experiences are linked to the later manifestation of mental disorders (Freud, 1957) and underscored in his theories the importance of early experiences for the entire life-span. Later, behavioral observations in animals, such as the famous studies of Harry Harlow and

coworkers (see Rosenblum, 1987) showing that early experiences, especially contact with the mother, have a strong impact on later behavior, expanded the knowledge about the relevance of experiences early in life. These findings stimulated further human research, such as, for example, that done by John Bowlby together with Mary Ainsworth on bonding and attachment, revealing that children show specific patterns of how they act and react in response to the presence or absence of caregivers (Ainsworth, Blehar, Waters, & Wall, 1978; Bowlby, 1958). As early as in the 1950s, animal researcher started to elucidate the biological underpinnings of long-term consequences of early adversities (e.g. Levine, 1957). However, it was only from the 1980s on that this field of research started to take off. Today, every week a number of new articles on animal studies are published, revealing new details about neurotransmitter changes related to experiences early in life.

For several years now, findings from animal studies have been the basis for studies in humans, where researcher have started to look at changes in neurotransmitter systems and hormones related to ACEs (for review see for example Heim & Nemeroff, 2002). The use of new technologies, especially brain imaging, has led to a better understanding of structural consequences and functional changes after ACEs (e.g. Bremner et al., 2003; for review, see Teicher et al., 2003). However, studies in humans are only at their beginning. In contrast to animal findings, there is only a crude knowledge about biological consequences of ACEs in humans. Major questions are still unanswered or have yet to be addressed. Among them is the question of why ACEs increase the vulnerability for such a great variety of mental disorders and physical illnesses (see Chapter 2). To better understand the role of ACEs in such disorders, it is important to examine further the great number of neurotransmitters and hormones that might be changed in relation to ACEs and ongoing stresses (see Charney & Manji, 2004).

Not all individuals who experience ACEs develop related mental disorders or physical illnesses, but we have only a very rudimentary knowledge about the psychobiological processes that enable these people to stay healthy in spite of ACEs. To understand this would be of paramount importance for the development of preventive actions.

Furthermore, even though studies have shown that some hormonal systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, are affected by ACEs (see Chapter 2), we do not know if these changes (in the hormonal system) are stable across different situations that the adult is confronted with and in which this biological system is activated, or if these changes depend on the environmental characteristics of the situations. Knowledge about this is crucial for a better understanding of the relevance of the biological changes. Moreover, this

might help to explain why certain individuals develop specific disorders related to ACEs, as the biological changes that are shown would depend on the adult environment the subject is living in.

Other important questions that need to be answered are related to the theoretical models underlying the long-term consequences of ACEs. Different models have been suggested for how ACEs can be related to their long-term psychobiological consequences. Models range from the interpretation of ACEs as "toxic agents" that destroy certain biological substrates, therefore hampering their function and leading to diseases, to early adversities as a source of meaningful information that is processed by the individual, to be used as a viable indicator for the future environment that helps the organism adapt in an optimal fashion. The more recent concepts have been termed behavioral, biological, developmental, environmental, or epigenetic programming and they have important implications for prevention and intervention (see Chapter 2 for details - see Barker, 1997; Bateson & Martin, 1999; F. Champagne & Meaney, 2001; Langley-Evans, 2004; Meaney, 2001; Rutter & O'Connor, 2004; Weaver et al., 2004; Weaver, Szyf, & Meaney, 2002). However, at least in humans, even though the concept of environmental programming is fascinating and very much in use, there is to date very little research or data that address the question of whether it really occurs in relation to ACEs.

Most research on the biological consequences of ACEs in humans has been focusing on biological systems that are usually related to stress or disease. However, animal and human studies have revealed a great variety of neurochemical, neuropeptide, and hormonal mediators that convey health protection and resilience (see Charney, 2004). In humans, we have only little knowledge about the effects of early positive and adverse experiences on the biological systems that are related to health promotion or mediation of resilience. As ACEs very often accompany the disruption of health-promoting systems (e.g., attachment, bonding, or social support) (House, Landis, & Umberson, 1988; Waters, Merrick, Treboux, Crowell, & Albersheim, 2000) it should be expected that in humans ACEs will have strong effects on biological systems mediating these processes.

1.2 SCOPE OF THE THESIS

In this thesis, findings are presented that address several of the topics outlined above. These results may lead to a better understanding of and a broader theoretical framework for the long-term psychobiological influences of early experiences. The presented research is strongly based on previous findings in animals and humans.

1.2.1 Objectives

Within the general goal of establishing a better understanding of the psychobiological consequences of ACEs and building a theoretical conceptualization of the processes involved, as outlined above, the more concrete objectives of the thesis are

(1) To scrutinize whether ACE-related changes in HPA-axis reactivity can be found in response to physical strain;

(2) To evaluate whether changes in sensitivity to arginine vasopressin (AVP), as a major regulator of the HPA-axis, can be found in relation to ACEs and stress during adulthood;

(3) To examine whether there are indications for changes in sensitivity to female sex hormones after ACEs, which could help to explain why ACEs lead to an increased risk for disorders for which female sex hormones presumably play a pivotal pathophysiological role; and

(4) To elucidate whether ACEs lead to changes in sensitivity to oxytocin (OT), which would be a first indicator that ACEs not only influence biological stress systems but also lead to changes in biological systems that have been related to health protection and mediation of resilience.

1.2.2 Hypotheses

Hypothesis 1: The HPA-axis is activated through different types of stimuli, including psychosocial stress and high-intensity physical exercise. Previous studies have shown that HPA-axis responses to psychosocial stress are increased in women with early sexual or physical abuse (Heim et al., 2000). However, whether the same changes could be seen after stimulation due to physical exercise was not known. Animal data have indicated that early adversities have different effects on HPA-axis reactivity, depending on the type of the HPA-axis-activating stimuli (Ladd et al., 2000). Therefore, the following hypothesis was tested: ***Women with ACEs in the form of physical and sexual abuse, compared to women without ACEs, show no increases in HPA-axis reactivity in response to physical exercise.***

Hypothesis 2: Besides corticotropin-releasing hormone (CRH), AVP is the major regulator of the HPA-axis at the level of the pituitary. Animal studies have shown that stress during different developmental phases influences the relative role of CRH and AVP in the control of the HPA-axis (De Goeij, Dijkstra, & Tilders, 1992; Kamphuis et al., 2002; Ma & Lightman, 1998; Rabadan-Diehl, Lolait, & Aguilera, 1995; Scott & Dinan, 1998; Volpi, Rabadan-Diehl, & Aguilera, 2004; Whitnall, 1989). Therefore, the following hypothesis was tested: ***In humans, stress early in life and/or adulthood chronic stress leads to changes in the sensitivity of the HPA-axis to AVP.***

Hypothesis 3: ACEs lead to an increased vulnerability for several disorders in which changes in HPA-axis activity as well as changes in sex hormone systems have been strongly suggested to be of relevance, such as major depressive disorder or premenstrual dysphoric disorder. Moreover, findings in animals suggest that early adverse experiences lead to changes in female sex hormone regulation (F. Champagne, Diorio, Sharma, & Meaney, 2001; F. A. Champagne, Weaver, Diorio, Sharma, & Meaney, 2003; Kaiser, Kruijver, Straub, Sachser, & Swaab, 2003; Kaiser, Kruijver, Swaab, & Sachser, 2003). Therefore, the following hypothesis was tested: ***ACEs lead to changes in HPA-axis sensitivity to female sex hormones.***

Hypothesis 4: ACEs lead to a disruption in processes, such as attachment and bonding, that have been related to stress protection, resilience, and promotion of health. A large number of animal studies and a few human studies have shown that OT is a major mediator of these processes and has stress-protective effects. Therefore, the following hypothesis was tested**:** ***ACEs lead to changes in the effects of OT on the HPA-axis.***

1.2.3 Approach

(1) The HPA-axis reactivity [adrenocorticotropin (ACTH) and cortisol] of adult women with and without ACEs in the form of sexual or physical abuse before menarche in response to a high-intensity bicycle ergometry was assessed and analyzed, including information about depressive symptomatology.

(2) Analyses of variance and multiple regression analyses were performed to identify whether in adult women, ACEs in the form of sexual or physical abuse before menarche and/or aspects of adulthood chronic stress predict ACTH and/or cortisol responses to exogenous application of AVP. Potential interfering factors were analyzed through repetition of the calculations in hold-out samples.

(3) Differences between adult women with and without use of oral contraceptives in overall ACTH and cortisol concentrations during an AVP stimulation test were compared between subjects with and subjects without ACEs in the form of sexual or physical abuse before menarche. Potential confounding factors were controlled through repetition of the calculation after alternative stratification with respect to the factors that might have influenced the findings.

(4) In a double-blind randomized placebo-controlled design, differences in salivary cortisol reactions to exogenous intransal OT versus placebo application were compared between healthy adults with and without ACEs in the form of parental separation before age 13.

1.3 Outline of the Thesis

The thesis is structured in the following way: After the introduction and the description of the objectives of the thesis in the present **Chapter 1**, the following **Chapter 2** presents the theoretical background on the topic, starting with a brief overview of the major types of ACEs, followed by the description of long-term effects of ACEs on the vulnerability for mental disorders and physical illnesses, and then presents the major biological findings in humans of changes related to ACEs. Characteristics of theoretical models of long-term consequences of early experiences are then presented and related to biological findings, mainly from studies in animals. **Chapter 3** presents our own findings on HPA-axis reactivity to physical stress in women with and without ACEs in the form of sexual or physical abuse. In **Chapter 4**, the role of AVP is scrutinized by presenting findings on the effects of ACEs in the form of sexual or physical abuse, as well as effects of adulthood stress, on the reactivity in an AVP stimulation test. **Chapter 5** presents data on the effects of the use of oral contraceptives on HPA-axis activity in women with and without ACEs in the form of sexual or physical abuse, as an indicator of the effects of ACEs on sensitivity to female sex hormones. In **Chapter 6**, data are presented from a study looking at differences in the sensitivity of cortisol to exogenous intranasal OT application between healthy adults with and without ACEs in the form of parental separation. Chapters 3–6 are always preceded by a preface, linking each chapter with the previous one, followed by an abstract of the present chapter. In **Chapter 7**, the findings from the previous four chapters are summarized and drawn together, followed by a general discussion of the findings, in **Chapter 8**, leading to an outlook, in **Chapter 9**. The book finishes with an overall abstract in English and German (Zusammenfassung).

Chapters 2–6 are written so that they can be read separately, in case the reader wants to be informed only on a certain aspect of the thesis. To make reading of a single chapter easier, abbreviations are introduced anew in each chapter.

CHAPTER 2

Theoretical Background

2.1 Overview of Major Types of Adverse Childhood Experiences

Adverse childhood experiences (ACEs) have profound and long-lasting effects on individuals. This has been repeatedly shown in a great variety of studies that assessed the long-term consequences of different types of ACEs (see Section 2.3). Children can suffer under a variety of different types of adversity. ACEs include general aspects of the living environment, such as growing up in families with low socioeconomic status, or growing up in poorer city quarters; adversities that are related to the primary caregivers, such as separation or divorce of the parents, death of a parent or close relative, mental illness of a parent (e.g. postpartum depression), separation from a parent due to other reasons (e.g. medical treatment in hospital), or untoward institutional rearing; adversities in the form of violence (sexual, physical, or emotional) or neglect; adversities due to specific single events, such as accidents; adversities related to negative influences of peer groups; and adversities in the form of events that affect a great number of individuals at the same time, such as natural disasters, catastrophes, famine, war, terrorist attacks, and others. Some children may suffer from a single ACE, such as divorce of the parents. Other children may suffer under multiple ACEs, for example, as a consequence of a major natural catastrophe, including death of the parents, witnessing of traumatic events, and long-term medical treatment under unfavorable conditions. ACEs can have long-term influences during all developmental stages, including the prenatal period (see for example Matthews, 2002; J. B. Young, 2002). The qualifier “adverse” is normative and applies to experiences that in most societies are seen as unfavorable and therefore should be prevented, if possible. Even though the term “adverse” can relate to a great variety of experiences, including mere physical threat (e.g. exposure to radiation), the main focus here lies on psychosocial adversities.

A large number of the ACEs outlined above have certain aspects in common that may underlie their long-term consequences. Five of these shared aspects, in particular, are thought to have long-term effects on behavior: (1) restrictions on the possibility of developing intense selective social relationships, (2) severe disruptions in the security of such relationships, (3) long-term threat to such relationships, (4) group influences of a maladaptive kind, and (5) the overall quality of adult–child interaction and communication (see Rutter, 2005). Interestingly, most of these aspects are in one way or another related to the quality of interpersonal relationships. In line with this, it has been shown that the effects of more general adversities, such as low socioeconomic status, are mediated through alterations in interpersonal relationship (i.e. parental care) (Conger, Ge, Elder, Lorenz, & Simons, 1994; McLoyd, 1998).