Long-term Psychobiological Consequences of Adverse Childhood Experiences:

Implications for Vulnerability and Resilience

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[A scientist] is a person who lives in the triangle which remains after the angle which we may call common sense has been removed from this four-cornered world.

Homage to Natsume Sōseki (1906/1965)

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ABBREVIATIONS

ACE	adverse childhood experience
ACE_dephigh	women with adverse childhood experience and clinically relevant levels of depressive symptoms
ACE_deplow	women with adverse childhood experience and no clinically relevant levels of depressive symptoms
ACEs_noOC	women with adverse childhood experiences without use of oral contraceptives
ACEs_noPTSD	women with adverse childhood experiences without comorbid posttraumatic stress disorder
ACEs_OC	women with adverse childhood experiences and use of oral contraceptives
ACEs_PTSD	women with adverse childhood experiences and comorbid posttraumatic stress disorder
ACTH	adrenocorticotropin
AKE	Aversive Kindheitserfahrungen
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AUCg	area under the curve with respect to ground
AUCi	area under the curve with respect to increase
AVP	arginine vasopressin
bpm	beats per minute
C	cytosine
cAMP/PKA	cyclic adenosine monophosphate/protein kinase A
CBG	cortisol binding globulin
CI	condition index
CON	controls
CRH	corticotropin-releasing hormone

CFS	chronic fatigue syndrome
CSF	cerebrospinal fluid
DELFIA	dissociation-enhanced lanthanide fluorescence immunoassay
DNA	deoxyribonucleic acid
DSI	Depression Status Inventory
EPS	early parental separation
ERα	estrogen receptor alpha
ERβ	estrogen receptor beta
ETI	Early Trauma Inventory
G	guanine
GAD	generalized anxiety disorder
GAD_{67}	glutamic acid decarboxylase$_{67}$
GR	glucocorticoid receptor
HHNA	Hypothalamus-Hypophysen-Nebennierenrindenachse
histone H3-K9	lysine-9 residue of H3 histone
HPA-axis	hypothalamic-pituitary-adrenal-axis
HR_{max}	maximum target heart rate
MDD	major depressive disorder
MR	mineralocorticoid receptor
MALDI-TOF-MS	matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
mRNA	messenger ribonucleic acid
NGFI-A	nerve growth factor-induced protein A
$N\text{-}H_3$	methyl group
noACEs_OC	women without adverse childhood experiences with use of oral contraceptives

noACEs_noOC	women without adverse childhood experiences without use of oral contraceptives
NS	not significant
OC	oral contraceptive
OT	oxytocin
PBMC	peripheral blood mononuclear cell
PSS	Posttraumatic Symptom Scale
PMDD	premenstrual dysphoric disorder
PND	postnatal day
PTSD	posttraumatic stress disorder
PVN	hypothalamic paraventricular nucleus
R^2	squared correlation of the predicted versus observed outcome in multiple regression
SAM	S-adenosylmethionine
SEM	standard error of the mean
SD	standard deviation
SDS	Self-Rating Depression Scale
STAI	State-Trait Anxiety Inventory
Stat5	signal transducer and activator of transcription 5
TAA	Trauma Assessment for Adults
TICS	Trier Inventory of Chronic Stress
VIF	variance inflation factor
5-HT	serotonin

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CHAPTER 1

Introduction and Objectives

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."***
>
> 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.