STRESS AND THE ADAPTIVE SELF-ORGANIZATION OF NEURONAL CONNECTIVITY DURING EARLY CHILDHOOD

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Abstract

A conceptual framework is proposed for a better understanding of the biological role of the stress-response and the relationship between stress and brain development. According to this, concept environmental stimuli (in children mainly psychosicial challenges and demands) excert profound effects on neuronal connectivity through repeated or long-lasting changes in the release of especially such transmitters and hormones which contribute, as trophic, organizing signals, to the stabilization or destabilization of neuronal networks in the developing brain. The increased release of noradrenaline associated with the repeated short-lasting activation of the central stress-responsive systems in the course of the stress-reaction-process to psychosocial challenges which are felt to be controllable acts as a trigger for the stabilization and facilitation of those synaptic and neuronal pathways which are activated in the course of the cognitive, behavioral and emotional response to such stressors. The long-lasting activation of the central stress-responsive systems elicited by uncontrollable psychosocial conflicts in conjunction with the activation of glucocorticoid receptors by the sustained elevation of circulating glucocorticoid levels favours the destabilization of already established synaptic connections and neuronal pathways in associative cortical and limbic brain structures. The facilitation and stabilization of neuronal pathways triggered by the experience of controllable stress is thus opposed, attenuated or even reversed in the course of long-lasting uncontrollable stress. This destabilization of previously established synaptic connections and neuronal pathways in cortical and limbic brain structures is a prerequisite for the acquisition of novel patterns of appraisal and coping and for the reorganization of the neuronal connectivity in the developing brain. Alternating experiences of repeated controllable stress and of long-lasting, uncontrollable stress are therefore needed for the „self-adjustment“ of neuronal connectivity and information processing in the developing brain to changing environmental (psychosocial) demands during childhood. The brain structures and neuronal circuits involved in the regulation of behavioral responding become thus repeatedly reoptimized and refitted, not to the changing conditions of life per se but rather to those conditions which are still able to activate the central stress response systems of an individual at a certain developmental stage**.**

1. A novel conceptual framework

Current stress research is characterized by fascinating insights into the mechanisms involved in the activation and the regulation of the neuroendocrine stress response and the consequences of this activation on the body and the brain. This progress is contrasted by a considerable degree of conceptual confusion. Until now, a generally accepted concept of stress is still elusive. Initially the term „stress" was used synonymous to „stressor" and no clear distinction was made between this stimulus and the reaction to it, the „stress-response". This concept has now been replaced by the recognition that stimulus and response can not regarded as two independent, stable entities but rather represent two closely linked components mutually affecting each other in the course of the stress-reaction-process. This conceptualization explicitly implies important aspects, such as the character of the strain, the appraisal and the psychological as well as the emotional changes which occur in the course of this process. It implies that, if an individual is able to terminate a certain stressor by his own efforts, a *controllable* stress response is elicited, whereas an *uncontrollable* stress response is initiated when no adequate coping strategies are available or can be applied to terminate the stressor. This distinction is closely related to Ursin´s concept of phasic and tonic activation[55] and provided the basis for a recently proposed novel conceptualization of the biological role of the stress response[26].

According to this concept, the stress-reaction-process is triggered by a physiological and/or psychosocial, imagined or anticipated strain and is characterized by a continuous interaction and adjustment between a multi-phase cognitive and emotional appraisal of the strain and its meaning for the individual, and a sequence of physiological, cognitive, emotional and behavioral reactions which allow coping with the situation. In the course of this process specific physiological, cognitive, emotional and behavioral changes will occur. Repeated experiences of controllable stress response favor the adaptation of an individual to its environmental demands through the stabilization and facilitation of appropriate patterns of appraisal and coping. The long-lasting neuroendocrine changes elicited in the course of an uncontrollable stress response favor the destabilization and extinction of inappropriate patterns of cognition and behavior and constitute therefore an essential prerequisite for the adaptative reorganization of neuronal networks and behavioral strategies. Alternating experiences of controllable and uncontrollable stress are needed for the acquisition of a most complex and flexible pattern of behavioral, emotional and cognitive strategies. Although far from being complete, this concept integrates and rearranges a multitude of empirical data published in recent years which show how adaptive modifications and reorganizations of neuronal connectivity are brought about in the course of the reactions to either repeated controllable or long-lasting uncontrollable stress (for review see[26]).

2. The controllability and uncontrollibility of stressors in experimental animals and humans

Most of our current knowledge on the consequences of the activation of the central stress responsive systems on the brain is derived from animal experiments using various kinds of physical stressors. The predominating stressors in the life of socially organized mammals and especially humans, however, are psychosocial conflicts. Psychosocial stress is not just

another, but a totally different kind of stress. The difference between physical (or physiological) and psychosocial (or psychological) stressors is a simple but fundamental one: Physiological stressors elicit a stress response because a certain objectively existing, environmental or physical force is strong enough to disrupt the counterregulatory mechanisms available to an individual (for a critical discussion of the role of psychological concomitants of physiological stimuli see[9,34]. Psychological stressors elicit a stress response because the subjective perception and interpretation of often rather subtle and ambiguous changes of the outer world come in flagrant variance with the expectations, beliefs or assumptions made by an individual on the basis of its previous experiences. Whereas physiological stress is caused by changes of the world outside the brain, the very root of psychological stress resides inside the brain: Whether or not and to what extent a stress response will be elicited, is dependent on a subject's interpretation of the changes perceived from its outside world.

If the previously acquired basic beliefs and assumptions of an individual about the world are incompatible with its current perception of this world, this individual will experience a sustained, more or less controllable, stress reaction until either its perception of the external world or its beliefs and assumptions about the world are corrected to better fit with one another. What may not always be evident in animal experiments using different kinds of physical stressors is therefore most obvious for the stress response elicited by psychosocial or psychological stressors in primates, and especially in humans:

1. The principal source and the principal target of this response is the brain, especially the higher cortical and limbic neuronal circuits and networks governing the ways by which we perceive, evaluate and interprete information from the world around us.
2. Both, the intensity and the duration of the central stress response and their long-term central consequences are dependent on the degree of controllability perceived by an individual over a certain kind of stressor.
3. The previous experiences of an individual are of uttermost importance in determining whether or not, and if yes, to what extent its central stress responsive systems will be activated by a certain stimulus.

The degree of controllability determines not only the severity of the stress response but also the balance between the adrenocortical and the sympathoadrenal mode of response. It has been reasoned that the SAM-system is preferentially activated when stressors appear to be controllable, whereas the HPA-system is predominantly activated when loss of control is experienced[15,25,57]. In general, animals with the ability to alter onset, termination, duration, intensity or pattern of aversive stimulation respond with lower glucocorticosteroid secretion than yoked control subjects without this ability[6,17]. Reinforcement and extinction of appetitive operant behavior differentially influence circulating noradrenaline, adrenaline and corticosterone: Food-reinforced lever pressing increases noradrenaline and decreases circulating corticosterone levels. Extinction is accompanied by decreasing noradrenaline and increasing corticosterone levels. These bidirectional changes in HPA and SMA-activity were interpreted to reflect the emotion-producing quality (positive or negative) of a shift (upward or downward) in the amount and/or frequency of reinforcement, rather than undifferentiated emotional arousal due to novelty of the new reinforcement schedule[15]. Levine[31] even defined stress as a "change in

expectancy developed during previously well-established behavior". He suggested that the absence of reinforcement under conditions where reinforcement has been continously present will lead to a stress response. In his model, three factors contribute to effective coping: (a) control or the ability to make a coping response, (b) feedback or information following the stimulus response and (c) predictability of the stressor. He, like others has designated "control" as the primary mechanism in their model of stress and coping, with the lack of control associated with helplessness.

In laboratory animals it is rather difficult to decide whether a given stressor is controllable. Very often, the term „chronic stress“ is used when animals are subjected to one and the same „stressor“ repeatedly for several days. This „chronic stress“ is not necessarily uncontrollable. Factors such as the nature, intensity, duration and frequency of stressful stimulation were shown to determine whether a process of sensitization or habituation predominates, or whether both processes balance out[27,45]. Typically, with the repetition of one and the same stressor for a certain period every day, the stress-induced elevation of plasma ACTH and/or glucocorticoid declines[30,46] . This habituation is stimulus-specific[5,27], intensity-dependent[40], and can only be prevented by increasing the intensity or by reducing the predictability of the stress paradigm applied[40,45] **.** Cognition, learning and the acquisition of behavioral coping strategies, which are facilitated by the repeated exposure to a controllable stressor, are primarily responsible for this effect. The more a subjective feeling of controllability over a certain type of stressor is acquired, the less likely the central stress responsive systems become activated upon reexposure to this or a similar type of stressor[27].

Only very few paradigms elicit long-lasting uncontrollable stress responses in laboratory animals. One of the models with highest overall validity of the effects generally observed - increased corticosteroid levels, lack of reactivity to an acute stress, psychomotor retardation, and failure to respond to pleasurable stimuli - is the daily exposure of rats to different stressful stimuli over a period of 21 days[28,58]. Because such treatments were invented and have been applied in order to demonstrate the negative, maladaptive, pathogenic consequences of uncontrollable stress on the brain, the interpretation of the findings is heavily prejudiced by this perspective. The possibility has never seriously been considered, that the behavioral, neurochemical and neuroanatomical consequences of uncontrollable stress may in fact be favourable for the survival of an individual when it is impossible to control a stressor. Resignation and passive behavior are the only alternatives left for a rat which is exposed to a never ending series of different uncontrollable stressors.

3. Controllable stress and the adaptive modification of neuronal networks

A controllable stress response is typically elicited when an individual has the subjective feeling that a certain demand or challenge can be met in principle by its own action but when this action is not (yet) ready, efficient or adequate enough to avoid the activation of his central stress responsive systems. The initial stages of the controllable and the uncontrollable stress response are identical. Both start with the recognition of a novel, unexpected, challenging or threatening stimulus which causes the generation of a nonspecific pattern of arousal in the associative cortex and in the limbic structures. Through descending excitatory efferences, this activation is propagated to lower brain structures, especially to the central noradrenergic system. If the stressor is felt to be uncontrollable, the arousal of the higher cortical and limbic brain structures will not only

persist but is even potentiated by the increased firing of noradrenergic afferences. Above a certain threshold, the sum of excitatory cortical and limbic, as well as of noradrenergic inputs to the neurosecretory hypothalamic nuclei will ultimately stimulate the release of corticotropin releasing hormone and vasopressin, and thus, activate the HPA-system and stimulate adrenal glucocorticoid secretion. However, if the stressor is felt to be controllable, the nonspecific pattern of arousal in the associative cortex will be funnelled into a specific activation of those neuronal pathways and circuits which are involved in the behavioral response to that stressor. Under these conditions, the enhanced noradrenergic output acts to facilitate the neuronal pathways activated in the course of this response. The reverbatory stimulation of the central stress responsive systems is no longer propagated, and the HPA-system is not at all or only slightly stimulated. Therefore, the controllable stress response may be regarded as an incompletely built up activation of the central stress responsive systems. It is characterized by a preferential activation of the central and the peripheral noradrenergic system.

Due to its extensive projections and the fact that adrenergic receptors are expressed not only by neurons but also by glial and endothelial cells, the central noradrenergic system is capable of modulating a great number of different brain functions:
Stimulation of neuronal adrenoreceptors increases the signal-to-noise ratio of cortical information processing, and contributes to the gating and to the facilitation of neuronal output patterns[14]. Stimulation of adrenergic receptors of cerebral blood vessels leads to enhanced perfusion, increased brain glucose uptake and elevated energy metabolism[8]. Activation of astrocytic adrenoreceptors stimulates glycogenolysis and the release of glucose and lactate[44,53] as well as the formation and the release of various neurotrophic factors[19,22]. Through these different effects, the increased noradrenergic output in the course of a controllable stress response contributes to the stabilization and facilitation of those neuronal pathways and connections which are activated in response to a certain controllable stressor. Repeated exposure to one and the same controllable stressor will thus lead to the successive facilitation of the neuronal circuitry involved in the behavioral responding. The noradrenaline-mediated stimulation of the synthesis and the release of neurotrophic factors by astrocytes will additionally favor structural adaptations through experience-dependent plasticity. Such stepwise adaptive modifications of the neuronal circuitry will automatically be triggered in the course of the controllable stress response until the original stressor can be adequately met by an efficient response. To some extent, this adaptive modification of associative cortical networks is comparable to catecholamine-mediated, peripheral structural adaptation processes, such as the increase of fur density in mammals upon repeated exposure to cold.
The particular importance of the repeated activation of noradrenergic neurons in the course of the response to controllable stress for central adaptation processes is further supported by the fact that specific mechanisms evolved in mammals which increase the output efficacy of the noradrenergic system in the course of future stress responses in individuals exposed to different kinds of controllable stressors . This upregulation of noradrenergic activity upon exposure to different controllable stressors is seen at several levels: The firing rate of noradrenergic neurons increases[43], the synthesis, storage, and release of noradrenaline by noradrenergic nerve endings rises[2,4,41], and even axonal sprouting and intensification of noradrenergic innervation in certain brain areas, e.g. in the cortex, have been observed[39]. Evidently, controllable stress of very complex and diverse character is a prerequisite for the optimal expression of the individual´s genetic potential and for the

elaboration of a very complex neuronal circuitry in the brain. An impressive illustration of the complex and persistent effects of multiple experiences of many different controllable stress responses on brain structure and brain function are the influences of „enriched environments“ on the development of the cortex of young experimental animals. Enriches environments provide many different stimuli which are novel and which can be explored. The recognition of novelty and exploratory behavior is always associated with cortical arousal and, increased firing of the central noradrenergic system[1,23], which may either escalate to cause a complete neuroendocrine stress response (if the novel stimulus appears dangerous) or which may resilenced by the recognition of harmlessness and therefore, controllability. Rats which had grown up under such complex stimulatory environments show a thicker cortex, enhanced vascularization, elevated number of glial cells, enlarged dendritic trees of pyramidal neurons, and an increased density of synapses in the cortex[24]. Additionally, in adulthood, they show diminished anxiety in novel environments and an increased response of their HPA-system under conditions of severe stress[3,33].

4. Uncontrollable stress and the adaptive reorganization of neuronal connectivity

An uncontrollable stress response is elicited when the activiation of the central stress sensitive systems cannot be terminated by an individual´s own efforts, because his previously acquired strategies of appraisal and coping are not appropriate or can not be employed. Under such conditions, the initial arousal of cortical and limbic structures will persist and contribute to escalate the reverbatory activation of the central stress responsive systems culminating in the activation of the HPA-system and adrenal glucocorticoid secretion. Because of their lipophilicity, circulating glucocorticoids can easily enter the brain and bind to the glucocorticoid receptors expressed by neurons and glial cells. As in the periphery, it is their main function to attenuate the activation of immediate stress responsive systems and to prevent these initial reactions from overshooting[36]. However, glucocorticoids do not directly suppress the immediate central responses in the course of the stress response , e.g., the release of excitatory amino acids or of monoamines. Instead, most actions of glucocorticoids in the brain are delayed and involve changes at the level of gene expression. These alterations have longer-lasting consequences on neuronal and glial cell function and metabolism. Certain functions will be affected in a way such that the targets of the immediate stress response are better protected against the potential damage caused by an overshooting future activation. This is achieved at several different levels: through the suppression of c-AMP formation in response to adrenergic stimulation[16,47], through compromising cerebral energy mobilization[18] or through the reduced formation of neurotrophic factors, growth of processes and synaptogenesis[12]. Glucocorticoids have been shown to potentiate the glutamate-induced damage to neurons and their dendrites[49] and are therefore able to interrupt the neuronal circuits involved in the initiation and propagation of the central stress response. The hippocampal pyramidal neurons are endowed with the highest density of glucocorticoid receptors and are therefore especially vulnerable to long-lasting elevations of circulating glucocorticoids caused by the uncontrollable stress[21,49,54]. Also the noradrenergic axons and nerve terminals in the cortex appear to be particularly susceptible under such conditions and tend to retract and to degenerate[38]. At the behavioral level, high concentrations of circulating glucocorticoids have been shown to facilitate the

extinction of previously acquired reactions[7,56]. The common feature of all these different effects caused by the activation of the HPA-system in the course of the uncontrollable stress response is their destabilizing influence on the previously established neuronal connectivity. The facilitation and stabilization of neuronal circuitry triggered in the course of previous controllable stress response is thus opposed, attenuated or even reversed in the course of an long-lasting uncontrollable stsress. The destabilization of the previously established neuronal connectivity in cortical and limbic brain structures may lead to fundamental changes in cognition, emotion and behavior and is therefore a prerequisite for the acquisition of novel patterns of appraisal and coping and for the reorganization of the neuronal connectivity in cortical and limbic associative networks (for a more detailed description of these phenomea see Huether [26]).

Alternating experiences of repeated controllable stress and of severe, long-lasting uncontrollable stress are needed for the „self-optimization“ of information processing in the brain and for the acquisition of a most complex and flexible pattern of appraisal and coping. Obviously, the stress reaction process is more than a simple mechanism to restore an acutely threatened homeostasis and the distinction between „eustress“ and „distress“ and between proadaptive and maladaptive consequences of stress is misleading. Because alternating experiences of controllable and uncontrollable stress are needed for the acquisition and facilitation of a characteristic individual pattern of appraisal and coping strategies which are optimally adjusted to the sum of previous experiences (and interpretations) of an individual, the experience of both, controllable and uncontrollable stress in the right quality, in the right intensity, in the right context and at the right age is a prerequisite of normal brain development.

4. The adaptive self-organization of neuronal connectivity and behavioral responsiveness during childhood

Throughout life, the repeated experience of the controllability of stressors is normally alternated by feelings of loss of control. The central adaptations resulting from the repeated exposure to controllable stressors are thus at least partly melted away during periods when the loss of control is experienced. The preliminary experimental evidence summarized above (and described in more detail elsewhere[26]) indicates that the activation of the central stress responsive systems by repeated experiences of controllable stress facilitates neuronal circuits and synaptic connections mainly through the activation of the central noradrenergic system. The neuroendocrine changes associated with the experience of uncontrollable stress, on the other hand, favor synaptic regression and the dissolution of previously established synaptic pathways and neuronal circuits. Consequently, an individual´s alternating experience of the controllability or uncontrollability of the conditions of its life establish or remodel, facilitate or dissolve the neuronal circuits and synaptic connections of the most plastic, most vulnerable, most associative parts of the brain. As long as the activation of the central stress system can be terminated by a cognitive, emotional or behavioral reaction, the neuronal circuits involved in this response become facilitated. If no cognitive, emotional or behavioral responses are available to terminate the activation of the central stress response system, the underlying neuronal networks become destabilized, thus providing novel opportunities for the reorganization of neuronal circuits and the acquisition of novel coping strategies for a more efficient control

of the novel environmental demands. The brain structures and neuronal circuits which are involved in the regulation of behavioral responses become thus repeatedly reoptimized and refitted, not to the changing conditions of life per se but rather to those conditions which are still able to activate the central stress response systems of an individual at a certain developmental stage**.**

The nature of what an individual considers life threatening, stressful challenges changes together with, and as a result of his improving sensory cognitive and intellectual realization of, and interaction with, the outside world. In infants, a stress response is initially only elicited in situations that demand the satisfaction of a basic need. Later, the central stress-responsive systems are most frequently activated by the recognition of certain social and cultural rules which prohibit the satisfaction of such a need. In the course of their socialization, individuals develop additional needs which are no longer basic but culturally acquired. The strategies which are chosen by an individual to meet each one of these challenges are strictly dependent on his previous experiences. „Successful“ behavioral strategies, i.e. the neuronal networks involved in the activation and execution of certain cognitive, emotional or behavioral reactions which make a certain type of stressor subjectively controllable, become increasingly reinforced and facilitated. Inadequate strategies which repeatedly fail to suppress and to silence the central stress responsive systems will either be eliminated or will become a constant source of dysregulation. By this self-optimization process, the cognitive, behavioral and emotional reactivity of an individual is fitted in a stepwise, trial-and-error manner to its changing environmental demands.

All newborns possess a certain repertoire of behavioral reactions which are activated in the course of, or together with, the activation of the central stress responsive systems when their homeostasis is threatened by cold, hunger, thirst etc. Thus, they all make the repeated early experience that their reactions are suited to terminate the central responses elicited by stressful experiences. This early recognition of the controllability of a stressor by an own action is one of the earliest associative learning experiences of a child and it has a strong imprinting impact on the developing brain. It is the prerequisite for the acquisition of an ever increasing repertoire of more and more specific and refined behavioral strategies for the control of stressors. This repeated experience of the controllability of stress is a prerequisite for the acquisition of behavioral strategies which allow an individual to act and not simply to react. The more successful these actions are, the more will the neuronal pathways and synaptic connections involved in a certain type of adaptive behavior become strengthened and efficient coping skills for certain types of stressors be developed. The ability to deal successfully with stressors strengthens the self-esteem and feelings of self-efficacy as much as the range of problem-solving skills of an individual. Consequently, the experience of the controllability of stress is the predominating experience and the driving force for the later development of those individuals of a social group which, within the sociocultural and age-specific context of this group, will become the most successful, the most clever, but not necessarily the most flexible and the most stable ones.

Such personal qualities emerge already at rather young ages. They can only be developed on the basis of secure stable affectional relationships during early childhood and favourable temperamental attributes. It is important, that stressful experiences are encountered at a time and in a way that allows the feeling of the controllability of stress to increase through appropriate responses. Reinforcing interactions with and responses from

other people are important prerequisites for the promotion of self-confidence and self-esteem. A child's ability to cope successfully with stress is therefore never due to the buffering effect of some supportive factor. Rather it is determined by its genetic predisposition and inherited temperamental attributes and by the chain of sequential experiences made under the prevailing conditions of a given familial and socio-cultural context.

5. Hereditary traits and the developmental modulation of stress responsiveness

Numerous examples are available which show that neuroendocrine reactivity to various stressors is influenced by genetic factors[32,51]. A typical example are the Roman rat lines which were selected on the basis of their performance in active avoidance behavior and which differ in a number of other behavioral and neuroendocrine characteristics as well[6]. Since the difference in the reactivity of the HPA-System to stress between these strains is only seen above a certain age, the quite obvious differences, such as in adrenal size or ACTH response to stress and CRF in adulthood, appear to be consequences of secondary adaptive modifications of the HPA-system to a primary genetic difference. Most likely, this genetic factor is expressed upstream of the HPA-system and affects the sensitivity of the mechanisms involved in the arousal of fear and anxiety and in the activation of the central stress system. This would also explain why genetic selection for avoidance conditioning using different strains and different settings does not necessarily result in consistent differences in adrenal size or reactivity of the HPA-System. Similar inconsistencies have been reported for differently stress-responsive mouse strains at the level of the monoaminergic systems involved in the propagation and regulation of the central stress response. These strains differ in their basal regional brain levels of noradrenaline, dopamine and serotonin. The stress-induced changes of amine levels and turnover vary with the strain of mice, the brain region and the particular transmitter and do not correlate with their different behavioral responsiveness to stressors[50].

It is widely assumed that molecular genetic analysis will allow to differentiate the trivial (secondary adaptive) from the important (primary genetic) correlates of the differential responsiveness of the central stress system. However, it is more likely that this strategy will rather identify a multitude of different genes which may, alone or in combination, determine the different responsiveness of an individulal to a given stressor. Some of these genes may be directly linked to individual components of the stress response but others may affect the responsiveness of the stress system indirectly through their primary effects on other mechanisms involved in homeostatic regulation of basic functions such as body temperature, blood sugar or energy metabolism. Such findings may help to explain otherwise confusing associations, such as between a genetic background of hypertension and the sensitivity to stressful stimulation[52], and confirm the important principle that any one of many genes can interfere with the central and neuroendocrine response to stressful stimulation and that the normal range of this response is orchestrated by many genes, each with small effects.

As evidenced by other contributions of this volume, adaptive modifications may occur at all levels of the developing stress responsive systems during pre- and postnatal life. They

may reach from the facilitation and reorganization of neuronal circuits in the associative cortical and limbic systems, they may include changes in the sensitivity and efficiency of the central monoaminergic or peptidergic system involved in the propagation and regulation of the central stress response and may reach to modifications of the responsiveness and the output of the hypothalamic hypophyseotropic system. The degree of plasticity, and therefore the adaptive potency, of these neural systems is highest during early stages of development and declines with increasing age. Therefore, the central stress responsive systems will be most easily modified and most permanently shaped by the experience of stress in early life. During this period, many of the mechanisms involved in the control of the initiation and propagation of the central stress response are still immature (e.g. incomplete monoaminergic and peptidergic innervation, immature cortical cytoarchitecture, ongoing synaptogenesis, etc.) or not yet developed (cognitive, emotional or behavioral coping strategies). Because the activation and propagation of the stress response is only inefficiently controlled and because the systems involved in the initiation and propagation of the central stress response are especially prone to adaptive modifications, the central stress system is particularly vulnerable to events occurring in early life. This fundamental principle is supported by an increasing number of research findings on the developmental modulation of the stress system. These studies consistently show that the development of the stress system is shaped by the experience of stress during early life. These effects are surprisingly robust and persist throughout life and they account, at least in part, for the individual differences seen in the responses to stressors in later life.

One example are the complex and long-lasting adaptations observed in adult rats which were removed from their mother and left alone in a separate cage for about 15 min. per day during the entire 21 days suckling period. This daily handling procedure elicits a stress reaction in these young animals, which is readily resilenced (and becomes „controllable“) when the pub is retoured to the mother’s care with all her liding and nursing in the familiar environment. At later ages, they exhibit reduced fearfulness in novel environments and a less pronounced increase in the secretion of adrenal glucocorticoids in response to a variety of stressors. Handled rats differ from their non-handled littermates also in the secretion of ACTH, in the efficiency of glucocorticoid-mediated feedback inhibition of the HPA response, in the number of glucocorticoid receptors in the cortex and the hippocampus and the amount of glucocorticoid receptor m-RNA expression in the hippocampus in hypothalamic CRF m-RNA content, CRF-levels in the median eminence and stress induced CRF-release (for review see[35] and contributions in this volume). The potentiation of the negative feedback sensitivity to glucocorticoids, and therefore, the attenuated HPA response to stressful stimulation persists throughout the animal’s life span[37,42].

Also in primates, the characteristics of the early social environment have long-term effects on the functional organization of the central stress system[11,29,34]. Even paradigms which produced only subtile alterations in the infant’s early experiences, such as peer rearing or experimental manipulations of the mothers’ foraging requirements, were shown to alter the basal activity of the HPA-system and the ACTH-response to stress in later life[13] and the balance between noradrenergic and serotonergic functioning in adulthood[48].

These and other findings have established the importance of early stressful experiences for the acquisition of cognitive emotional and behavioral coping strategies in later life. They support the notion that the associative neuronal circuits of the cortical and limbic brain are extremely plastic and can most easily and most permanently be modified during the period

of immaturity, when they are not yet completely elaborated. For methodological reasons, these structural changes in neuronal connectivity and cytoarchitecture are difficult to demonstrate in cortical and limbic structures where they are most likely to occur. Paradoxically they can be detected in better organized areas such as the cerebellum even though this structure is probably much less affected by the rearing conditions[20].

It can be expected that the increasing application of brain imaging techniques will provide a more detailled knowledge about the full spectrum of possible adaptive changes in the structure and the function of the human brain which may be caused by an inadequate balance between controllable and uncontrollable stress experiences in early life. Such studies are currently performed in children and adults with a early history of severe uncontrollable stress experiences (detachment, loss, sexual abuse and other kinds of early trauma). They ought be complemented by studies in children and adults who, due to a preponderance of one and the same controllable challenge during earlier life periods, aquired inappropriate feelings of mastery (narcissistic personalities) or developed specific forms of neurotic and personality disorders.

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