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Joint influence of early life stress and intranasal oxytocin on stress reactivity:

Insights from brain connectivity

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Deutsche Zusammenfassung

Unser Alltag ist durch unterschiedlich starke Stresserfahrungen geprägt. Eine angemessene neuronale und physiologische Stressreaktivität und -regulation ist daher sehr wichtig für das körperliche und seelische Wohlbefinden. Frühe Stresserfahrungen, z.B. das Erleben emotionaler oder körperlicher Misshandlung in der Kindheit, haben nachhaltigen Einfluss auf Stressreaktionen im Erwachsenenalter. Das Neuropeptid Oxytocin hat einen angst- und stressreduzierenden Effekt. Aus bisherigen Studien ist bekannt, dass der Effekt einer intranasalen Oxytocinapplikation bei Personen mit frühen Stresserfahrungen verändert ist. Jedoch bleibt bislang unklar, wie frühe Stresserfahrungen und Oxytocin interagieren, als auch, welche neuronalen Mechanismen daran beteiligt sind.

Das Ziel der vorliegenden Dissertation lag darin, (1) den Einfluss von frühen Stresserfahrungen auf an der Stressregulation beteiligte neuronale Netzwerke im Gehirn zu untersuchen, (2) die Rolle dieser Netzwerke bei der Interaktion von frühen Stresserfahrungen und Effekten der intranasalen Oxytocinapplikation zu charakterisieren.

In Studie I wurden mittels funktioneller Magnetresonanztomographie (fMRT) die Effekte früher Stresserfahrungen und intranasaler Oxytocinapplikation auf die funktionelle Konnektivität der Amygdala im Ruhezustand untersucht. In Studie II wurde psychosozialer Stress während einer fMRT-Messung experimentell induziert. Die Daten wurden dann mittels psychophysiologischer Interaktionsanalysen (PPI) ausgewertet, um Rückschlüsse darauf zu ziehen, wie stressinduzierte Veränderungen der funktionellen Konnektivität der Amygdala durch die Interaktion von frühen Stresserfahrungen und intranasaler Oxytocinapplikation moduliert werden.

Die Hauptbefunde sind wie folgt:

(1) Frühe emotionale Missbrauchserfahrungen sind mit einer reduzierten funktionellen Konnektivität zwischen der Amygdala und dem prägenualen anterioren Cingulum (pgACC) im Ruhezustand assoziiert. Diese Amygdala-pgACC Konnektivität im Ruhezustand geht wiederum mit einem erhöhten Angstempfinden nach psychosozialer Stressinduktion einher.

(2) Bei Probanden mit gering ausgeprägten frühen Stresserfahrungen ist eine stärkere Amygdala-pgACC-Konnektivität mit einer stärkereren stressinduzierten Deaktivierung im pgACC assoziiert. Diese Interaktion zwischen Ruhezustand und Stressreaktionen im pgACC wird durch Oxytocin abgeschwächt. Bei Probanden mit einer stärken Belastung durch frühe Stresserfahrungen zeigt sich eine reziproke Interaktion zwischen Ruhezustand und Stressreaktionen im pgACC. Zudem zeigte sich hier kein signifikanter Oxytocineffekt.

(3) Akuter Psychosozialer Stress verändert die funktionelle Konnektivität zwischen der Amygdala und weiteren Gehirnarealen, die an Salienzprozessen und der Kontrolle von autonomen und endokrinen Systemen beteiligt sind. Eine stressinduzierte Verstärkung der Konnektivität zwischen Amygdala und Hippocampus ist mit frühen Erfahrungen von emotionalem Missbrauchs assoziiert.

(4) Dieser positive Zusammenhang zwischen frühen Erfahrungen emotionalen Missbrauchs und stressinduzierter verstärkter Amygdala-Hippocampus-Konnektivität wird durch die intranasale Oxytocinapplikation vermindert. Dabei zeigt sich nach Oxytocin Applikation eine negative Korrelation zwischen funktioneller Amygdala-Hippocampus-Konnektivität und der Cortisolreaktion auf Stress.

Unter Bezugnahme auf das Modell der Allostase und der allostatischen Belastung wurde in der vorliegenden Dissertation die Hypothese aufgestellt, dass die individuellen Stressregulationssysteme durch das Erleben früher Stresserfahrungen nachhaltig

verändert werden können. Die vorliegenden Befunde bekräftigen die Ergebnisse früherer Untersuchungen dahingehend, dass frühe Stresserfahrungen die limbische-präfrontale Konnektivität nicht nur im Ruhezustand, sondern auch während experimentell induziertem psychosozialen Stress beeinflussen. Die hier dargestellten Studien zeigen jedoch erstmalig, dass frühe Stresserfahrungen und Oxytocineffekte interagieren und die stressinduzierte Verstärkung der Amygdala-Hippocampus-Konnektivität beeinflussen. Die Änderungen der Konnektivität im limbisch-präfrontalen Netzwerk werden als Ausdruck einer geänderten Stressregulation im zentralen Nervensystem interpretiert. Die vorliegenden Befunde sollten bei zukünftigen Entwicklungen zur therapeutischen Anwendung von Oxytocin, die auf dessen stressmildernden Effekt abzielen, Berücksichtigung finden.

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Summary

Stress occurs often in everyday life to various degrees. Appropriate neural and physiological stress responses are crucial for our survival and well-being. Stressful experience in early life has long-lasting influence on stress reactivity in adulthood. The neuropeptide oxytocin (OXT) is found to alleviate stress responses. However, the stress-attenuating effect of intranasal OXT is altered in individuals who have experienced early life stress (ELS). The neural underpinnings of the interaction between ELS and OXT remain unclear, though.

The overall aim of the present dissertation was therefore to investigate the impact of ELS on neural circuitries involved in stress regulation, and to explore neutral circuitries associated with the interplay between ELS and OXT.

In study I, resting-state functional magnetic resonance imaging (rs-fMRI) was used to investigate the effects of ELS and intranasal OXT on amygdala-centered resting-state functional connectivity (rs-FC). In study II, psychophysiological interaction (PPI) analysis was performed on fMRI data collected during acute psychosocial stress to examine the joint influence of ELS and intranasal OXT on stress-induced changes in amygdala-centered FC.

The main results are:

(1) Early life experience of emotional abuse predicts reduced rs-FC between amygdala and pregenual anterior cingulate cortex (pgACC), which in turn predicts stress-induced elevation in state anxiety.

(2) In subjects with lower ELS scores, stronger pgACC-amygdala rs-FC associates with stronger stress-induced pgACC deactivation, and this rest-task interaction is attenuated

by OXT. In subjects with higher ELS scores, this rest-task interaction is reversed and OXT has no significant effect.

(3) Acute psychosocial stress induces large-scale FC changes between amygdala and brain regions involved in salience processing and autonomic-neuroendocrine control. Stress-induced enhancement in amygdala-hippocampal FC is positively predicted by early life experience of emotional abuse.

(4) This positive association between emotional abuse and amygdala-hippocampal FC during acute psychosocial stress is moderated by intranasal OXT. Amygdala-hippocampal FC after the administration of intranasal OXT correlates negatively with cortisol stress responses.

Based on animal studies, the model of allostasis and allostatic load has proposed that ELS changes the set point of stress regulation systems in the brain and body. Our findings in human subjects corroborate this theoretical framework of ELS by demonstrating the impact of ELS on functional coupling within the limbic-prefrontal circuitry both at resting state and during acute psychosocial stress. It is also the first study in human subjects to report the joint modulation of ELS and intranasal OXT on transient limbic FC changes during acute stress. Altered functional dynamics within the limbic-prefrontal circuitry may indicate an altered set point of stress regulation in the central nervous system, and need to be considered when developing therapeutic interventions based on the stress-attenuating effect of OXT.

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List of Abbreviations

ACTH - adenocorticotropine hormones

ANS - the autonomic nervous system

BOLD - blood oxygenated level dependent

CRH - corticotropin releasing hormone

CTQ - Childhood Trauma Questionnaire

DMPFC - dorsomedial prefrontal cortex

ELS - early life stress

FC - functional connectivity

FFG - fusiform gyrus

fMRI - functional magnetic resonance imaging

GAS - General Adaptive Syndrome

GRs - glucocorticoid receptors

HPA - hypothalamic-pituitary-adrenocortical

MIST - the Montreal Imaging Stress Task

mPFC - medial prefrontal cortex

MRs - mineralocorticoid receptors

MRI - magnetic resonance imaging

OXT - oxytocin

pgACC - pregenual anterior cingulate cortex

PHG - parahippocampal gyrus

PN - the parasympathetic nervous system

PNS - the peripheral nervous system

PPI - psychophysiological interaction

PVN - paraventricular nucleus

ROI - region of interest

rs - resting state

rs-FC - resting-state functional connectivity

sgACC - subgenual anterior cingulate cortex

SNS - the sympathetic nervous system

SPC - signal percent change

Chapter 1. General Introduction

Human beings face various challenges from an ever-changing physical and social environment. Stress occurs when the challenges are perceived as taxing or exceeding one's ability to cope. Stress is a mental state that involves intricate brain and bodily responses. It influences how we perceive, what we pay attention to, what we memorize, and which decisions we make. Stress responses often act as a double-edge sword. On the one hand, they help to reallocate resources and energy, which promote adaptation and survival in a short range of time. On the other hand, stress responses can become a cumulative burden when they are prolonged, repeated, or dysregulated, especially during early years of life. The dysregulation and accumulation of stress has a significant impact on both physical and mental health. For this reason, the neural and physiological mechanisms for stress regulation, accumulation and intervention have nowadays become an increasingly important topic for psychologists, neuroscientists, and psychiatrists.

The present dissertation aims at investigating the interplay between the brain circuitries involved in stress regulation, the accumulation of stress during early years of life, and the intervention of stress responses via intranasal oxytocin. The first chapter begins with a brief review of stress models in physiology and psychology, focusing on the neuroendocrine mechanisms of stress regulation that are crucial for the accumulation of stress. This is followed by a summary of animal and human evidence on the influence of early life stress on adult endocrine stress responses. Chapter 1 then introduces the stress-attenuating effect of intranasal oxytocin, focusing on inconsistent findings that are partly contributed by early life stress. Based on these perspectives, I formulate the overall aims of the present dissertation and the research questions addressed by empirical studies reported in chapter 3 and 4.

1.1 Stress: fast, slow, and accumulative stress responses

1.1.1 Evolution of stress models in physiology and psychology

Physiological stress

The concept 'stress' was first used in engineering in the late 17th century as a measure of the destructive pressure acting upon man-made structure (e.g. bridges) (see the work of Robert Hooke cited in Hinkle, 1973). Hooks' analysis of stress has motivated analogous concepts in the field of biology and biomedicine. According to Walter B. Cannon (1871-1945), physical changes in the external environment trigger coordinated physiological processes in the organism to maintain a stable internal equilibrium of the body (e.g. stable blood sugar level or body temperature). Such steady states in the body, called *homeostasis*, are vital to the survival of the organism (Cannon, 1929). The rapid and adaptive reactions prompted by threats to maintain homeostasis (so called the *fight-or-flight* responses) are mediated by activation of the sympathetic nervous system (SNS) and secretion of catecholamines such as norepinephrine or epinephrine. The notion *homeostasis* is a centerpiece in the conceptual framework of modern stress theory. Within this framework, stressors are environmental events that threaten homeostasis. Stress responses are adaptive reactions that maintain and restore homeostasis. Stress denotes a state in which environmental perturbation exceeds the organism's ability to maintain homeostasis (Selye, 1984).

Following Cannon's work, Hans Selye (1907-1982) has proposed the model of *General Adaptive Syndrome* (GAS). According to Selye (1984), physical stressors trigger a slow, non-specific response of the body that consists of three stages: an initial alarm reaction, a prolonged resistance and a terminal stage of exhaustion leading to organismic death. This slow, non-specific stress response is mediated by activation of the hypothalamic-

pituitary-adrenocortical (HPA) axis and secretion of corticosteroids (glucocorticoid and mineralocorticoid). The GAS model is a cornerstone in modern stress theory. It dissects stress responses into different stages along a longer time course with differential health consequences. The GAS model has led to a line of research on how prolonged stress and activation of stress hormones (especially glucocorticoids) influence stress regulation system itself and other brain functions. This has inspired later research in modern neuropsychiatry that associated stress reactivity with mental health.

Psychological stress

The establishment of 'stress' as a psychological concept is indebted to works by John W. Mason (1924-2014) and Richard S. Lazarus (1922-2002), who have pointed out that stressors triggering GAS can be psychological as well as physical. Lazarus (2006) has emphasized individual differences in stress processing and highlighted the role of appraisal and coping. The stress concept in psychology denotes the relationship between the person and the environment. The mental state of stress occurs, when a person (1) is physically or psychologically challenged by environmental demands, (2) perceives the situation as personally significant, and (3) appraises the challenge as taxing or exceeding ones' resources for coping. Psychological stressors include novel, uncertain, or unpredictable events, anticipations of unpleasantness, harm or loss, as well as psychosocial factors like threat to self-identity or interpersonal relationship (Mason, 1975). The *Social Self-Preservation Theory* by Dickerson et al. (2004) has further describe psychosocial stressors as events in the social environment that threatens one's social value, esteem and status. A recent meta-analysis within the same theoretical framework has confirmed that psychological stressors also activate the HPA axis and the secretion of cortisol (glucocorticoid produced in humans), and relative large effect size has been observed in psychosocial stress tasks inducing both uncontrollability and social-

evaluative threats (negative evaluation by others) (Dickerson & Kemeny, 2004). Psychological models of stress emphasize the individual differences in the appraisal and coping of stress and add a developmental perspective. It is suggested that these individual differences in stress reactivity are predisposed by genetic background and shaped by learning and experience.

Biopsychological allostasis and allostatic load

The theory of *allostasis and allostatic load* by Bruce McEwen (Karatsoreos & McEwen, 2011; McEwen, 1998) has proposed an integrated framework to describe the mechanisms employed to maintain physiological or psychological homeostasis through active intervention (adaptive plasticity). *Allostasis* denotes adaptation via change: coordinated physiological responses (*allostatic responses*) maintain and restore homeostasis by actively and adaptively changing the set point of homeostasis. Allostatic responses are mediated by multiple factors in the autonomic, neuroendocrine and immune system that interact with each other. *Allostatic load* denotes the cost of adaption and describes the cumulative burden on brain and body after prolonged or poorly regulated allostatic responses. Early experience of repeated and excessive activation of the stress regulation system can lead to a changed set point of homeostasis, which promotes survival for a short range of time. However, the changed set point of the stress regulation system in early life can also lead to altered stress regulation in adulthood and become a potential risk for physical and mental health (McEwen, 2003). The model of allostasis and allostatic load lays the theoretical groundwork for examining effects of early life stress and its impact on the development of stress reactivity.

1.1.2 Stress regulation in central and peripheral nervous systems

Stress responses are mediated by coordinated physiological processes in both the central and peripheral nervous system, and these multiple waves of stress responses act in distinct time windows.

Autonomic nervous system: the rapid stress responses

In the peripheral nervous system (PNS), the autonomic nervous system (ANS) mediates the most rapid responses to stressors via its sympathetic and parasympathetic branches. For example, the sympathetic nervous system (SNS) increases heart rate and blood pressure within seconds after stressor onset via its innervation to the cardiovascular system, while the parasympathetic nervous system (PN) exerts opposite actions reflexively (Ulrich-Lai & Herman, 2009). With balancing actions in the SNS and the PN, ANS stress responses are rapid but short lived (i.e. initiated within seconds and normalized within 30 to 60 minutes) (Hermans et al., 2014).

Hypothalamus-pituitary-adrenal axis and the limbic-prefrontal circuitry: the slow stress responses

Activation of the hypothalamic-pituitary-adrenal (HPA) axis mediates relatively slow but long-lasting stress responses. Upon the perception of stressors, the hypothalamic paraventricular nucleus (PVN) secretes corticotropin releasing hormone (CRH). CRH stimulates the release of adenocorticotropine hormones (ACTH) from the anterior pituitary into the system circulation. ACTH binds to receptors in the adrenal cortex and promotes synthesis and secretion of glucocorticoids (Ulrich-Lai & Herman, 2009) (see Figure 1.1). Unlike norepinephrine and epinephrine produced by the ANS, glucocorticoids can cross the blood-brain-barriers, and glucocorticoid stress responses are characterized by a sluggish time course (Droste et al., 2008). For example, rodent

evidence has shown that hippocampal glucocorticoid concentration increases slowly, reaches maximum level 30 - 50 minutes after stressor onset, and can last for hours depending on the type of stressor (Droste, et al., 2008). The HPA axis is orchestrated by coordinated activations in several interconnected brain regions, including the amygdala, hippocampus, and prefrontal cortex (Herman et al., 2005). The HPA axis and the limbic-prefrontal brain regions are major target for glucocorticoids. As the end product of HPA activation, glucocorticoids form a negative-feedback loop and terminate HPA activation by binding to receptors in the pituitary gland, hypothalamic PVN, as well as amygdala, hippocampus, and the prefrontal cortex (Herman, et al., 2005; Ulrich-Lai & Herman, 2009) (see Figure 1.1).

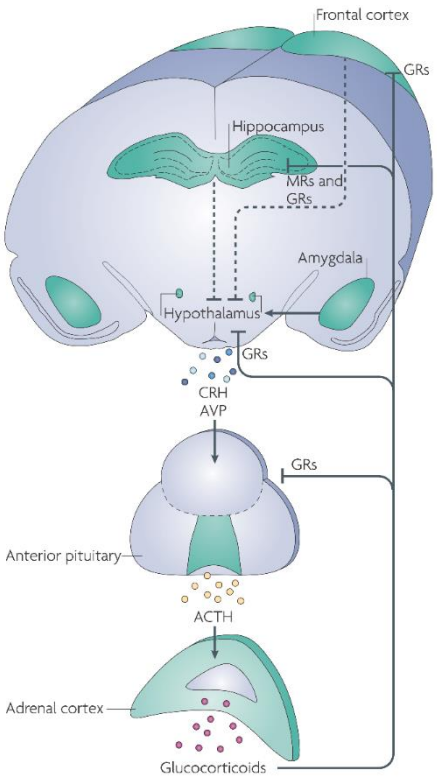

Figure 1.1 Hypothalamus-pituitary-adrenal axis and the limbic-prefrontal circuitry (Lupien et al., 2009)

ACTH, adenocorticotropine hormones; AVP, arginine vasopressin; CRH, corticotropin releasing hormone; GRs, glucocorticoid receptors; MRs, mineralocorticoid receptors.

At the cellular level, glucocorticoids have both a non-genomic effect and a much slower genomic effect (Gunnar & Quevedo, 2007; Hermans, et al., 2014). The non-genomic effect enhances neural excitability in amygdala and hippocampus, interacts with ANS activation, and has been associated with processing salience information related to stressors. For the genomic effect, activated glucocorticoid receptors triggers downstream intracellular mechanisms and alters gene transcription of several proteins that are involved in stress regulation and related neuronal functions. During the sluggish time course of glucocorticoid elevation in the brain, the genomic effect may continue to exert effects on the limbic-prefrontal brain areas and the HPA axis for prolonged periods. For this reason, the glucocorticoid genomic effect has been proposed to be a key mediator of cumulative stress and allostatic load, especially during early years of life (Gunnar & Quevedo, 2007).

1.2 Early life stress and the development of stress reactivity

Substantial evidence shows that environmental factors such as the experience of early life stress (ELS; e.g. emotional/ physical neglect or abuse) can cause persisting changes in the autonomic, neuroendocrine and immune system, and shape individual differences in stress regulation (Carpenter et al., 2007; Carpenter et al., 2010; Carpenter et al., 2009; for reviews, see Heim & Binder, 2012; Strüber et al., 2014). Early life stress (ELS) is the excessive or prolonged activation of the stress regulation system during early years of life while the stress regulation system itself is still developing. The current model of ELS, based on both animal work and human research, focuses strongly on psychosocial stressors, especially adverse relationships between the young individuals and their caregivers. In animal work, ELS is modeled by separation between the pup and the mother, or experimental manipulation of the quality of maternal care (e.g. the frequency of grooming and licking in rodents) (Harrison & Baune, 2014). In human research, ELS is

characterized by a spectrum of adverse social experiences that occur before puberty, including sexual, physical, and emotional forms of abuse, physical and emotional neglect, witnessing crime or violence, as well as separation from parents (Pechtel & Pizzagalli, 2011). These adverse social experience are stressors by themselves which exceed the coping resources of the young individuals. Moreover, it has been shown that a warm, supportive and stable relationship with caregivers plays critical role in regulating stress hormone production during the early years of life, forming a buffer against other environmental stressors (Loman & Gunnar, 2010). The lack of a sensitive caregiver (neglect) or the presence of an abusive caregiver (abuse) may demolish such buffer, thereby prolonging the impact of other environmental stressors and aggravating the allostatic load.

Animal models have shown that neural circuits responsible of stress regulation are malleable throughout early childhood and puberty (Lupien, et al., 2009). Dysregulation of the HPA axis is suggested to be primed by ELS experience. Retrospective human studies have shown stable associations between experience of ELS and altered endocrine stress responses in adulthood, characterized by either hyper- or hypo- activation of the HPA axis, accompanied by excessive or blunted cortisol stress responses (Carpenter, et al., 2007; Carpenter, et al., 2009; Heim & Binder, 2012; Loman & Gunnar, 2010; Strüber, et al., 2014). A longitudinal study has associated ELS during infancy and preschool period with either hyper- or hypofunctioning of the HPA axis in adolescence depending on the type of ELS (Essex et al., 2011). Among children exposed to ELS, the alteration in HPA function is closely associated with severity of mental health symptoms in adolescence (Essex, et al., 2011). However, the neural mechanisms underlying the effects of ELS on endocrine stress responses have been explored only recently.

ELS has been associated with altered gray matter volume and cortical thickness in brain regions that are involved in stress regulation, including the dorsolateral and ventromedial prefrontal cortex, hippocampus and amygdala (Hart & Rubia, 2012; Kelly et al., 2013; Tottenham, 2012; Tottenham et al., 2010). There is also evidence for deficits in structural interregional connectivity among these regions, suggesting altered neural networks (Choi et al., 2009; Hart & Rubia, 2012). Limbic-prefrontal regions like the amygdala, hippocampus and the medial prefrontal cortex (mPFC) form an important regulatory circuit that helps to optimize behavioral and physiological reactions towards adversity (Pezawas et al., 2005). The impact of ELS on functional connectivity within the limbic-prefrontal circuitry remains unclear.

1.3 Oxytocin and its stress-attenuating effect

The neuropeptide oxytocin (OXT) is an evolutionarily conserved hormone that acts both on the peripheral nervous system (PNS) and as neuromodulator in the central nervous system (CNS). OXT is synthesized in the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus. OXT enters the PNS via the axonal projections to the pituitary gland, where it is secreted into the peripheral circulation. In the CNS, OXT is secreted through dendritic release into the extracellular space, and reaches other distal brain regions like mPFC and amygdala via diffusion. In addition, smaller parvocellular neurons in the PVN also synthesize OXT and project directly to other brain regions, including the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis and brain stem (Meyer-Lindenberg et al., 2011) (see Figure 1.2).

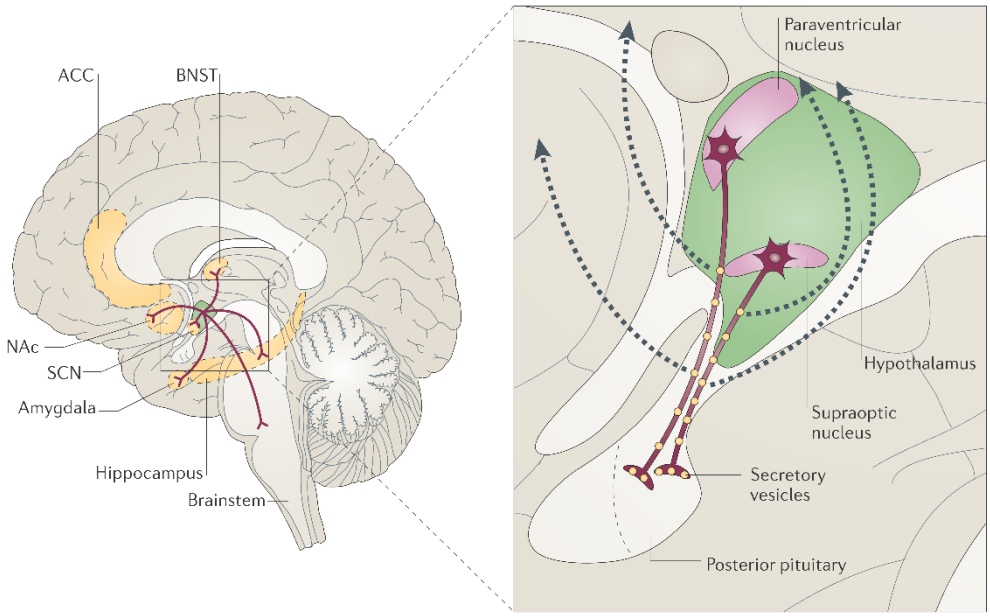

Figure 1.2 The secretion and diffusion of endogenous oxytocin (Meyer-Lindenberg, et al., 2011)

ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; NAc, nucleus accumbens; SCN, suprachiasmatic nucleus.

OXT administered via intranasal spray might reach the PNS and the CNS via different delivery routes (Quintana et al., 2015). It has been suggested that intranasal OXT can assess the amygdala from deposition on the olfactory epithelium, through the olfactory bulb then via axonal projections as well as diffusion through CSF. OXT delivered through olfactory and trigeminal pathways is also suggested to stimulate the production of endogenous OXT from the PVN.

Experiments on rodents and non-human primates show that endogenous and intranasal OXT can inhibit HPA stress responses (Neumann et al., 2000; Parker et al., 2005). The administration of intranasal OXT in human subjects has been shown to alleviate cortisol responses to psychosocial stress (de Oliveira et al., 2012; Ditzen et al., 2009; Heinrichs et al., 2003; Linnen et al., 2012). Based on these findings, intranasal OXT has been proposed as a novel pharmacological intervention for stress-related symptoms in various

psychiatric diseases including social phobia (Epperson et al., 1996; Guastella et al., 2009; Labuschagne et al., 2010; Macdonald & Feifel, 2013; Pitman et al., 1993). However, in individuals who experienced ELS, the stress-attenuating effects of OXT seem to be altered (Meinlschmidt & Heim, 2007). A recent meta-analysis has summarized studies on intranasal OXT administration on cortisol stress responses in laboratory tasks (Cardoso et al., 2014). It has been shown that the overall effects size of the stress-attenuating effect of intranasal OXT is modest and not statistically significant, with moderate heterogeneity across studies. For this reason, caution has been raised regarding further translation of intranasal OXT as anxiolytic intervention in clinical application (Bakermans-Kranenburg & van IJzendoorn, 2013). There is also a growing body of evidence showing that ELS also modulates other prosocial effects of intranasal OXT, such as empathy and cooperation (Riem, Bakermans-Kranenburg, et al., 2013; van Ijzendoorn et al., 2011). However, it remains unclear whether the neural circuit underlying stress regulation is also involved in the interplay between ELS and OXT.

1.4 Rationale for hypotheses: amygdala in stress regulation, ELS accumulation, and OXT administration

Among the brain regions involved in stress regulation, the amygdala and its connection with other frontolimbic areas plays a crucial in both the embodiment of ELS and the stress-attenuating action of OXT. Structural connectivity between the amygdala and the ventromedial / orbital prefrontal cortex, other limbic areas, as well as striatum has been supported by evidence from non-human primates (Amaral & Price, 1984) and human diffusion tension imaging study (Bracht et al., 2009). The pattern of amygdala-centered structural connectivity has been further corroborated by findings in amygdala-centered functional connectivity, based on resting-state fMRI (Roy et al., 2009), meta-analytic connectivity modeling (Bzdok et al., 2013), and anti-correlation pattern in cortical

thickness (Albaugh et al., 2013). Connectivity between the amygdala, hippocampus and the prefrontal cortex plays important role in the top-down regulation of HPA activation and the negative feedback of glucocorticoids. Hippocampus and medial prefrontal cortex have been proposed to be the major inhibition sites for HPA activation, while the amygdala has been suggested to be an integration site for both inhibitory and excitatory inputs (Herman, et al., 2005; Ulrich-Lai & Herman, 2009).

There has been further evidence from longitudinal studies tracing children to adolescence, supporting that ELS can derail the developmental tract of amygdala, resulting in altered morphology and activity (Tottenham, 2012; Tottenham, et al., 2010). Meanwhile, consistent with animal models, a recent immunohistochemical study has confirmed that oxytocin receptors are also present in the central and basolateral regions of the amygdala in the human brain (Boccia et al., 2013). FMRI studies have shown changes in amygdala activation after intranasal OXT administration (Lischke et al., 2012; Riem et al., 2012; Rilling et al., 2014; Rilling et al., 2012). A recent study has examined pharmacodynamic profile of intranasal OXT in the human brain using imaging of in vivo cerebral blood flow (Paloyelis et al., 2014). The temporal profile has revealed sustained changes in cerebral blood flow with a peak response at 39 - 51 min after OXT administration. The special profile has delineated a network involved in intranasal OXT action, including areas like the caudate, striatum, amygdala, hippocampus, hypothalamus, anterior and middle cingulate cortex, as well as anterior insula.

Taken together, substantial evidence supports that amygdala, itself being a crucial integration site in CNS stress regulation, may also be a central target for the joint modulation of ELS and OXT.

1.5 Research Aims

The primary aims of the present dissertation are (1) to examine the impact of ELS on functional coupling within the brain circuitries underlying stress regulation, and (2) to investigate the involvement of the brain's stress regulation circuitries in the interplay between ELS and OXT.

In the first study we investigated the effect of ELS on amygdala-centered rs-FC, and examined whether ELS-associated changes of rs-FC in the limbic-prefrontal circuit predict its response to psychosocial stress. We further explored the joint effect of OXT and ELS on the amygdala-prefrontal circuit (Chapter 3).

In the second study we investigated the effect of ELS and OXT on transient changes of amygdala-centered functional connectivity induced by acute psychosocial stress, and explored the association between the amygdala-centered functional connectivity and cortisol stress responses (Chapter 4).

Chapter 2. General Methodology

To assess functional coupling within a given brain circuitry, we acquired functional magnetic resonance imaging data and estimated functional connectivity strength both at resting state and during a psychosocial stress task. Chapter 2 provides a brief introduction to the functional magnetic resonance imaging technique and the rationale for adopting two indices of brain connectivity, i.e. intrinsic and reflexive functional connectivity.

2.1 Mapping brain structure and activity

Magnetic resonance imaging (MRI) is a powerful noninvasive neuroimaging technique. MRI can capture the anatomical structure of the brain in relatively high-resolution and forms the basis for functional MRI (fMRI), which measures brain activity in vivo. Both methods are now widely applied for assessing normal and pathological brain function (Toga & Mazziotta, 2002).

For structural MRI, the source of signal relies on the interaction between external electromagnetic force and the proton in the hydrogen atom. Like other elementary particles, the proton carries an intrinsic form of rotational momentum called *spin*, which gives the proton a *magnetic dipole moment*. Such magnetic dipole moment can interact with external magnetic fields. In an MRI scanner, the external magnetic field (B_0) causes the spins to align with the magnetic field. Turning on an additional RF pulse promotes the spins from a lower energy state (aligned) to a higher energy state (antialigned), causing the longitudinal magnetization (align with B_0) to be tipped into the transverse plane (e.g. 90^o to the direction of B_0). Immediate after RF excitation, the spins begin to reestablish the equilibrium since they prefer the lower energy state that is aligned with B_0. The time needed for the longitudinal magnetization to recovery to its maximum value is called longitudinal relaxation time (T1). In a given sample volume (voxel), the number

of spins of interest (e.g. protons in hydrogen atoms) are different. Different brain tissues like gray matter, white matter, cerebral spinal fluid have different T1, enabling the T1-weighted image to tell different brain structures apart (Toga & Mazziotta, 2002).

For functional MRI (fMRI) to capture activities in the human brain in vivo, it is assumed that neural activity is associated with localized changes in oxygen consumption. Such changes in oxygen consumption is reflected in a relative increase in oxyhemoglobin and decrease in deoxyhemoglobin in activated brain areas. Hemoglobin is diamagnetic when oxygenated, and paramagenetic when deoxygenated, giving rises to different *transverse relation time* (time for spins to recover to zero along the transverse plane, T2*) in different location of the brain. This signal of a T2*-weighted image, called the blood oxygenated level dependent (BOLD) signal vary according to the degree of oxygenation, which is an indirect representation of distributed maps of brain activity (Toga & Mazziotta, 2002).

2.2 From brain activity to brain connectivity

Traditional analyses of fMRI focus on the presence of activation foci in certain local brain areas under experimental manipulation. Analyses of local activation have largely contributed to our understanding of functional specialization of the brain (e.g. visual or sensorimotor processes). However, analyzing brain activation in a spatially segregated way tells us little about the integration within and between functionally specialized areas, this is compensated by analyzing functional or effective connectivity of the brain (Friston, 2011). Functional connectivity describes the statistical dependencies among remote neurophysiological events. It relies on correlations among measures of neuronal activity, e.g. BOLD signal in different brain areas in the case of fMRI, and it has no assumption on the direction of functional coupling. Effective connectivity, in contrast, models the influence that one neural system exerts over another and needs hypotheses on direction of the coupling. In short, functional connectivity measures functional coupling that can

be quantified with measures of statistical dependencies, e.g. correlation or coherence; whilst effective connectivity represents a model that tries to explain observed functional connectivities.

2.3 Integrating intrinsic and reflexive brain connectivity

Analyses of both brain activity and brain connectivity can be performed on fMRI data acquired both during resting state and during task manipulation. Resting state denotes a state without external demand of tasks. Brain activity and connectivity at resting state represents the intrinsic aspect of brain function (Raichle, 2010). Even in the absence of explicit input, output, or goal-directed thoughts, the brain is still active for ongoing information processing, which interprets, responds to, and predicts environmental demands. Resting-state functional connectivity (rs-FC) represents intrinsic functional dynamics of a certain brain circuitry that are trait-like or at basal status without being manipulated by tasks. It has been shown that patterns of rs-FC are linked closely with the white matter structure of the brain (van den Heuvel et al., 2009). Brain activity and connectivity evoked by certain task manipulation represents the reflexive view of brain function (Raichle, 2010). Although strong correspondence has been found between task-evoked and resting-state brain functions (Mennes et al., 2010; Mennes et al., 2011), weak correspondence has also been demonstrated in regions where patterns of evoked functional dynamics are more adaptive and context dependent (Mennes et al., 2013). Task-evoked FC differences are supposed to reflect transient changes in brain circuitry coupling in response to task modulation. It has been proposed that the full repertoire of brain function during task performance is characterized (1) by an intrinsic basal state that is also present during resting state, and (2) by evoked task-general and task-specific changes in activity and connectivity (Cole et al., 2014). Appreciating the full repertoire

of functional dynamics in a given brain circuity requires both resting-state and task-based functional connectivity analyses.

Chapter 3. Early Life Stress Modulates Amygdala-Prefrontal Functional Connectivity: Implication for Oxytocin Effects [1]

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Chapter 4. Amygdala-Hippocampal Connectivity Changes during Acute Psychosocial stress: Joint Effect of Early Life Stress and Oxytocin [1]

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Chapter 5. General Discussion

In this final chapter, findings reported in chapter 3 and 4 are summarized and discussed in relation to previous research on ELS within the framework of the allostasis and allostatic load model. Synthesizing our findings and previous evidence, I propose a tentative model to address the role of intrinsic and reflexive limbic-prefrontal connectivity in early life stress accumulation and stress intervention. In the end, I discuss several lines of future research needed for the confirmation, refinement and enrichment of this model.

5.1 Integration of findings

5.1.1 Modulation of limbic-prefrontal functional coupling by ELS

The first aim of the present dissertation was to investigate the impact of ELS on functional coupling in the neural circuitry underlying stress regulation. To identify functional connectivity patterns within the brain's stress regulation circuitry, the amygdala was selected as seed-region given its crucial role as an integration site for both inhibitory and excitatory inputs in the stress regulation circuitry, and as an action site for modulating ANS and HPA stress responses (Herman, et al., 2005; Ulrich-Lai & Herman, 2009). To fully capture the functional dynamics within the amygdala-centered brain networks, two indices providing compensatory information have been used. Intrinsic brain connectivity, measured in study I via rs-FC strength, represents trait-like spontaneous coupling within the stress regulation circuitry at basal level (see Chapter 3). Association between rs-FC strength and task-evoked activation in prefrontal regions represents the rest-task interaction within prefrontal-amygdala circuit. Rest-task interaction can be viewed as a product of a dynamic functional system in which evoked activity is influenced by previous basal state. Reflexive brain connectivity, assessed in study II (Chapter 4) via

task-evoked FC changes, represents transient shifts within the stress regulation circuitry in response to the demand of acute psychosocial stress.

Intrinsic amygdala-prefrontal functional coupling

Our studies have two main findings related to this aim. Concerning intrinsic brain connectivity indicated by rs-FC, results of the first study show that experience of emotional abuse in early life predicts decreased rs-FC between right amygdala and pgACC (see Figure 5.1A). Heightened trait anxiety and elevated stress-induced state anxiety were observed as ELS scores increases. Decreases in pgACC-amygdala rs-FC strength predict stress-induced state anxiety increases and pgACC deactivation. Based on previous findings of animal models and human neuroimaging studies, medial prefrontal cortex including pgACC is a crucial regulatory site over amygdala activity and downstream physiological stress responses (Dedovic, D'Aguiar, et al., 2009; Dedovic, Duchesne, et al., 2009; Herman, et al., 2005; Kern, et al., 2008; Pruessner, et al., 2008; van Marle, et al., 2010; Veer, et al., 2011). Both gray matter morphology and white matter trajectory within the prefrontal-amygdala circuit have been shown to be susceptible to the impact of ELS (Hart & Rubia, 2012). Findings of longitudinal studies have associated stress dysregulation with altered prefrontal-amygdala functional dynamics in children and adolescents who have experienced ELS (Burghy, et al., 2012; Gee, et al., 2013; Herringa, et al., 2013). Adding to these previous findings, our study highlights an association between ELS, pgACC-amygdala rs-FC and subjective report of stress reactivity in adulthood.

Moreover, ELS modulates how pgACC-amygdala rs-FC associates with stress-induced pgACC deactivation (see Figure 5.1B). In study I we observed that stronger pgACC-amygdala rs-FC predicted stronger pgACC deactivation in subjects with lower ELS scores; whilst in subjects with higher ELS scores, stronger pgACC-amygdala rs-FC

predicted weaker pgACC deactivation. The medial prefrontal cortex (including supragenual ACC, pregenual ACC and subgenual ACC in humans) exerts delicate and fine-grained regulation over the amygdala, which is crucial for the experience and regulation of negative arousal (Pezawas, et al., 2005). Previous animal models of stress and anxiety have proposed that medial prefrontal cortex (with prelimbic and infralimbic cortex as homologous structures in the rodent brain) regulates the excitatory and inhibitory balance in the amygdala at a tonic level. For example, after ibotenic acid lesion in the prefrontal cortex, rats show imbalance in glutamatergic / GABAergic tone in the amygdala at tonic level, which correlates to elevated fear and anxiety (Gonzalez et al., 2004). Our findings show that pgACC-amygdala rs-FC can predict subsequent task evoked-pgACC deactivation, and this rest-task interaction is modulated by ELS. These findings suggest that ELS is not only associated with changes in intrinsic functional coupling in the limbic-prefrontal circuitry, but also with an altered functional transition from basal to task-evoked states in the pgACC.

Reflexive amygdala-hippocampal connectivity

Regarding reflexive brain connectivity, acute psychosocial stress induces FC enhancement between bilateral amygdalae and distributed cortical-subcortical regions that are associated with salience processing, autonomic-neuroendocrine control, attentional reorientation and executive functions. Among them, stress-induced FC enhancement between bilateral amygdalae and the right hippocampus / parahippocampal gyrus is predicted by early life experience of emotional abuse. The hippocampus plays an important role in inhibiting HPA activation and is one of the major targets of glucocorticoid negative feedback and its genomic effect (Klengel, et al., 2013). Amygdala-hippocampal connectivity is not only crucial for CNS stress regulation (Ulrich-Lai & Herman, 2009), but also an important relay for stress-related memory

encoding and retrieval (Richter-Levin & Akirav, 2000). Adding on the previous evidence, our study II suggests that ELS is also associated with altered reflexive connectivity shifts in the amygdala-hippocampal circuit in response to psychosocial stress (see Figure 5.1C).

ELS-associated changes in limbic-prefrontal connectivity: stress-regulation circuitries with an altered set point

The limbic-prefrontal circuitry plays crucial role in stress regulation in the central nervous system. Coordinated functional coupling within the limbic-prefrontal circuitry modulates HPA stress responses (Ulrich-Lai & Herman, 2009). Altered limbic-prefrontal coupling is associated with dysregulated stress responses. For example, decreased structural and functional connectivity between pgACC and amygdala is associated with trait, state, and pathological anxiety (for review, see Kim, Loucks, et al., 2011). Enhanced amygdala-hippocampal FC correlates inversely with cortisol stress responses and is involved in prolonged aftermath of stress (Vaisvaser, et al., 2013). Based on animal models of cumulative stress, limbic-prefrontal regions are key sites in the negative-feedback loop of glucocorticoid and malleable by glucocorticoid's genomic effect (Klengel, et al., 2013). It is hence proposed that the limbic-prefrontal circuitry may be involved in the impact of ELS on stress reactivity (McEwen & Morrison, 2013). Previous neuroimaging studies in humans have reported ELS effects on limbic-prefrontal morphology and activity. From a perspective of brain connectivity, our findings extend previous research and lend support to the impact of ELS on limbic-prefrontal functional coupling, both at resting state and during acute psychosocial stress. The model of allostasis and allostatic load has proposed that ELS changes the set point of stress regulation systems. Corroborating this theoretical framework, our findings of ELS-associated alteration in continuous and dynamic limbic-prefrontal coupling may indicate an altered set point of stress regulation systems in brain.

5.1.2 Interaction between ELS and OXT on limbic-prefrontal functional coupling

The second aim of this dissertation was to explore the involvement of the limbic-prefrontal circuitry in the interplay between early life stress and intranasal oxytocin. In study I, we didn't observe significant effects of OXT on amygdala-centered rs-FC itself. However, ELS and OXT jointly modulated the association between pgACC-amygdala rs-FC and stress-induced pgACC deactivation (see Figure 5.1D). Moreover, study II revealed an interaction effect between ELS and OXT on transient changes in amygdala-hippocampal FC in response to acute psychosocial stress (see Figure 5.1E). Specifically, early life emotional abuse positively predicts stress-induced enhancement in amygdala-hippocampal FC in the placebo session, whilst this positive association is moderated in the oxytocin session. Stress-induced FC changes in the amygdala-hippocampal circuit is negatively associated with cortisol stress responses in the oxytocin session. Previous studies indicate that oxytocin attenuates endocrine stress responses, such as reducing stress-induced changes in salivary cortisol level (Heinrichs, et al., 2003). Further studies reveal that such stress-attenuating effect of oxytocin is moderated or even reversed in subjects who have experience ELS (Grimm, et al., 2014; Meinlschmidt & Heim, 2007). Amygdala is also a crucial action site of intranasal OXT, given its dense expression of oxytocin receptors (Boccia, et al., 2013) and its altered activation after intranasal OXT (Riem, van Ijzendoorn, et al., 2013; Riem, et al., 2012; Rilling, et al., 2014; Rilling, et al., 2012). Recent studies reported joint modulations of ELS and OXT on amygdala activity during psychosocial stress (Grimm, et al., 2014). Adding to this evidence, our findings are the first to report joint modulatory effects of ELS and intranasal OXT on (1) functional transition from basal to task-evoked states in the pgACC-amygdala circuit, and (2) transient stress-induced FC shifts in the amygdala-hippocampal circuit.

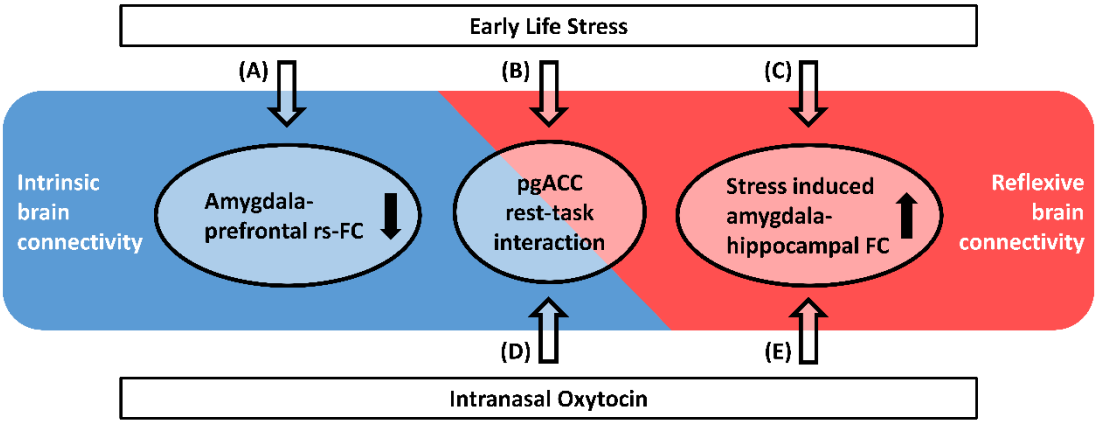

Figure 5.1 Summary of main findings. (A) ELS predicts decreased amygdala-prefrontal rs-FC; (B) ELS modulates rest-task interaction in the pgACC; (C) ELS predicts increased stress-induced amygdala-hippocampal FC enhancement; (D) joint effects of ELS and intranasal OXT on pgACC rest-task interaction; (E) joint effects of ELS and intranasal OXT on stress-induced amygdala-hippocampal FC enhancement.

ELS, early life stress; OXT, oxytocin.

5.1.3 Effects of intranasal oxytocin on stress-regulation brain circuitries with an altered set point

Based on animal studies, the model of allostasis and allostatic load has proposed that ELS changes the set point of stress regulation systems in the brain and body (Karatsoreos & McEwen, 2011; McEwen, 2012). Our findings in human subjects corroborate this theoretical framework of ELS. The impact of ELS on limbic-prefrontal functional coupling is evident (1) by the index of intrinsic brain connectivity at resting state, and (2) by the index of reflexive brain connectivity changes during acute psychosocial stress. It is revealed that altered reflexive changes in limbic-prefrontal functional connectivity may be involved in the interplay between ELS and intranasal OXT. Taken together, our findings suggest that altered continuous and dynamic functional coupling in the limbic-prefrontal circuitry may indicate an altered set point of stress regulation systems in the

central nervous system. One may further speculate that this altered set point of stress regulation system may underlie altered sensitivity to stress interventions such as intranasal oxytocin.

5.2 Perspectives

This tentative model suggest important brain pathways that are involved in the interplay between stress accumulation in early life, stress regulation and intervention in adulthood. Merits of the model include integrated measurements of intrinsic, reflexive brain connectivity and rest-task interaction, as well as implications for altered sensitivity to the stress-attenuating effect of intranasal oxytocin. However, there are potential caveats regarding our findings, and this tentative model needs further confirmation, refinement and enrichment by future studies.

First, we used retrospective measure of ELS, and the subjectivity of this measure needs to be acknowledged when interpreting the findings. Recent longitudinal studies have reported similar effects of ELS on limbic-prefrontal functional connectivity in children and adolescences (Burghy, et al., 2012; Gee, et al., 2013; Herringa, et al., 2013). Animal models manipulating mother-pup relationships during early age also lend further support to the contribution of ELS on the development of limbic-prefrontal circuitry. However, it remains clear how genetic predisposition modulate the impact of ELS on stress reactivity. Since limbic-prefrontal functional coupling is also modulated by genetic variances like polymorphisms of the serotonin transporter gene (Pezawas, et al., 2005). It is possible that individual difference in limbic-prefrontal coupling represents a predisposition for vulnerability or resilience to ELS. This needs to be clarify by future studies investigating brain circuits before the occurrence of early life stressors, as well as by gene x environment interaction studies.

Second, our studies are based on healthy young subjects without concurrent psychiatric symptoms. Although this help to control for the confounding effect of concurrent symptoms and history of medication, it is not known whether the subjects will develop psychiatric disorders later in life. Future longitudinal studies on both healthy and clinical sample are needed to identify individuals who are vulnerable and resilient to the impact of ELS, and to identify compensatory changes in emotional functioning despite the absence of concurrent psychiatric symptoms.

Third, our studies focused on the impact of ELS on stress reactivity itself. Our tentative model proposed that altered limbic-prefrontal connectivity may represent an altered set point of the stress regulation systems in the brain. One of the proposed theory suggest that the altered set point in stress regulation systems may render the individuals more susceptible to accumulation of stress in late life and to aging-related degenerative changes (Ridout et al., 2015). However, another line of research describe the impact of stress on cognitive function and memory with an inverted-U shape model (Luksys & Sandi, 2011; Qin et al., 2012). In line with this hypothesis, altered stress regulations systems (e.g. changes in limbic-prefrontal connectivity and cortisol stress responses) may be either beneficial or disadvantageous depending on the exact task of cognition and memory. Future studies are needed to clarify whether an altered set point in stress regulation systems is beneficial, compensatory or deleterious.

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Appendix A. Supplementary Material for Chapter 3[1]

[1] The supplementary material for Chapter 3 was published as online supplement data for

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[1] The supplementary material for Chapter 4 was published as online supplement data for

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Curriculum Vitae [1]

[1] Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.

Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorligende Arbeit selbständig und nur unter Verwendung der angegebenen Quellen und Hilfsmittel erarbeitet und verfasst habe. Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Berlin, den 20. Apr. 2015

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