Characterizing the Dynamic Multilevel Stress Response and its Influence on Cognitive Emotion Regulation

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Abstract

Numerous studies emphasize the pivotal role of stress in the development and maintenance of various mental and somatic disorders. Despite this growing field of research, the specific mechanisms how stress affects psychological well-being remain elusive. Hereby, stress research is considerably challenged by the complexity of the concept at hand: stress is commonly considered a complex phenomenon involving multiple response systems and dimensions and exerting a variety of short- and long-term effects on the brain and the body. This dissertation aimed at providing a detailed characterization of the multidimensional stress response and its determinants (Study 1). In a second step we investigated the effect of stress on subsequent psychological processes, here emotion regulation (Study 2).

In concrete, Study 1 focused on the effect of long-term hypothalamus-pituitary-adrenal axis activation (as assessed in hair cortisol concentration (HCC)) on acute stress reactivity. Acute stress reactivity was assessed in all its complexity on multiple response levels: on a psychological level (i.e. changes in self-reported affective state), on an endocrine level (i.e. changes in saliva cortisol concentration), on a neural level (i.e. changes in Blood-oxygen-level-dependent (BOLD) responses), and on a physiological level (i.e. changes in heart rate). For laboratory stress induction, the Scan*STRESS*-C was implemented and validated. The Scan*STRESS*-C provides a short psychosocial stress protocol combining mentally challenging arithmetic tasks with socio-evaluative elements. Results proved the Scan*STRESS*-C to be effective in eliciting significant stress responses on all response levels. Moreover, acute stress responses on endocrine and neural level were negatively associated with HCC, indicating blunted stress reactivity in individuals with high levels of long-term cortisol secretion. The latter finding is further discussed in the light of stress immunization processes based on recent or chronic stress exposure.

In Study 2, the Scan*STRESS*-C was applied to investigate the effect of acute multilevel stress responses on subsequent emotion regulation in a between-group design. Given the importance of intact emotion regulation abilities to adequate psychosocial functioning and long-term mental health, knowledge of whether and how emotion regulation shows impairments in the face of stress can further advance psychological and psychiatric research. To test emotion regulation abilities in the aftermath of the Scan*STRESS*-C, we used the Cognitive Emotion Regulation Task (CERT), a picture-based

paradigm assessing both reappraisal and distraction of aversive negative pictures. Self-reported emotional state ratings as well as BOLD-responses to the pictures served as dependent variables. Interestingly, while the Scan*STRESS*-C again effectively elicited stress responses on multiple response levels in the stress group, emotion regulation abilities did not differ between the stress and the control group, neither in self-report, nor in brain activity during the CERT. This result indicates that both reappraisal and distraction abilities survive the aftermath of a laboratory psychosocial stressor. Previous literature suggests that the relationship of stress and emotion regulation may be more complex, even bidirectional, depending on a multitude of intrapersonal (e.g. habitual reappraisal, fatigue) and contextual (e.g. timing, stressor intensity) factors.

Taken together, the key messages of this dissertation are two-fold: first, it provides a detailed characterization of the dynamic multilevel stress response by introducing an eligible and reliable stress protocol for in-MR use, i.e. the Scan*STRESS*-C. Second, it contributes significantly to understanding the complex interplay of stress and emotion regulation, incorporating ambiguous results of previous studies. In the broader context of resilience research, this dissertation serves to identify the mechanisms underlying stress-related mental dysfunctions and thereby to inform preventive and therapeutic interventions.

Zusammenfassung

Stress spielt nachweislich eine ausschlaggebende Rolle bei der Entstehung und Aufrechterhaltung diverser mentaler und somatischer Erkrankungen. Trotz des steigenden Forschungsinteresses sind die spezifischen Mechanismen, wie Stress das psychische Wohlbefinden beeinflusst, nach wie vor ungeklärt. Eine große Herausforderung für die Stress-Forschung stellt die Komplexität des vorliegenden Konstrukts dar: Stress gilt als ein komplexes Phänomen, das mehrere Antwortsysteme und -dimensionen umfasst und eine Vielzahl von kurz- und langfristigen Auswirkungen auf das Gehirn und den Körper ausübt. An dieser Stelle knüpft die vorliegende Dissertation an, indem zunächst eine detaillierte Charakterisierung der multidimensionalen Stressantwort und ihrer Determinanten vorgenommen wurde (Studie 1). In einem zweiten Schritt wurde die Wirkung von Stress auf nachfolgende psychische Prozesse, hier die Emotionsregulation, untersucht (Studie 2).

Studie 1 untersuchte konkret den Effekt der langfristigen Aktivierung der Hypothalamus-Hypophysen-Nebennieren-Achse (gemessen mit Cortisol-Konzentrationen im Haar (HCC)) auf die akute Stressreaktivität. Hierbei wurde die akute Stressreaktivität in ihrer ganzen Komplexität auf mehreren Reaktionsebenen erhoben: auf psychologischer Ebene (d.h. Veränderungen des selbstberichteten affektiven Zustands), auf endokriner Ebene (d.h. Veränderungen der Cortisol-Konzentration im Speichel), auf neuraler Ebene (d.h. Veränderungen der BOLD-Antwort) und auf physiologischer Ebene (d.h. Veränderungen der Herzfrequenz). Zur Stressinduktion im Labor wurde der Scan*STRESS*-C implementiert und validiert. Der Scan*STRESS*-C stellt ein kurzes psychosoziales Stressprotokoll dar, das mental-herausfordernde Rechenaufgaben mit sozio-evaluativen Elementen kombiniert. Die Ergebnisse zeigten, dass der Scan*STRESS*-C auf allen Reaktionsebenen signifikante Stressreaktionen auslöste. Darüber hinaus waren die akuten Stressantworten auf endokriner und neuraler Ebene negativ mit HCC-Werten assoziiert, was auf eine reduzierte Stressreaktivität bei Personen mit hoher Langzeit-Cortisol-Sekretion hinweisen könnte. Die Ergebnisse werden weiterführend im Kontext von Stressimmunisierungsprozessen diskutiert.

In Studie 2 wurde der Scan*STRESS*-C angewandt, um die Wirkung der akuten Stressreaktion auf nachfolgende Emotionsregulationsprozesse zu untersuchen. Der Emotionsregulation kommt im Kontext psychosozialer Funktionsfähigkeit und langfristiger psychischer Gesundheit eine große Bedeutung zu. Somit kann das Wissen darüber, ob und

wie akuter Stress die Emotionsregulation beeinträchtigt, die psychologische und psychiatrische Forschung weiter voranbringen. Um Emotionsregulationsfähigkeiten nach dem Scan*STRESS*-C zu testen, verwendeten wir den Cognitive Emotion Regulation Task (CERT), ein bildbasiertes Paradigma zur Erhebung von Neubewertungs- und Ablenkungsprozessen infolge aversiver negativer Bilder. Als abhängige Variablen fungierten sowohl selbstberichtete Veränderungen des emotionalen Zustands sowie die BOLD-Antworten auf die Bilder. Die Ergebnisse zeigen, dass zwar der Scan*STRESS*-C in der Stressgruppe erneut erfolgreich eine Stressreaktion auf mehreren Reaktionsebenen auslöste. Jedoch unterschieden sich die Emotionsregulationsfähigkeiten zwischen der Stress- und der Kontrollgruppe interessanterweise nicht (weder in den selbstberichteten Emotionsratings noch in der Gehirnaktivität während des CERT). Dieses Ergebnis deutet darauf hin, dass die Neubewertungs- und Ablenkungsfähigkeiten unbeeinträchtigt von den Folgen eines psychosozialen Labor-Stressors sein könnten. Bisherige Studien zu diesem Thema lassen vermuten, dass die Konstrukte Stress und Emotionsregulation einer komplexen, bidirektionalen Beziehung unterliegen und von vielen intrapersonellen (z.B. gewohnheitsmäßige Neubewertung, Müdigkeit) und kontextuellen (z.B. Timing, Stressorintensität) Faktoren beeinflusst werden.

Zusammenfassend lassen sich zwei Kernaussagen dieser Dissertation festhalten: Zum einen konnte durch die Einführung eines validen Stressprotokolls (Scan*STRESS*-C) eine detaillierte Charakterisierung der dynamischen mehrdimensionalen Stressreaktion vorgenommen werden. Zum anderen konnte wesentlich zum Verständnis des komplexen Zusammenspiels von Stress und Emotionsregulation beigetragen und dabei die mehrdeutigen Ergebnisse früherer Studien integriert werden. Im breiteren Kontext der Resilienzforschung unterstützt diese Dissertation die Identifikation jener Mechanismen, die stressbedingten psychischen Dysfunktionen zugrunde liegen und fördert somit die Entwicklung präventiver und therapeutischer Interventionen.

List of Abbreviations

AAL	Automated Anatomical Labeling
ACTH	Adrenocorticotropic Hormone
ANOVA	Analysis of Variance
AUCi	Area Under the Curve (respect to increase)
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent
CERT	Cognitive Emotion Regulation Task
CBT	Cognitive Behavioral Therapy
CG	Control Group
CRH	Corticotropin-Releasing Hormone
CPT	Cold Pressure Task
dACC	Dorso-Anterior Cingulate Cortex
dlPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
EMA	Ecological Momentary Assessment
EMG	Electromyography
EPI	Echo Planar Imaging
ER	Emotion Regulation
FB	Feedback
fMRI	Functional Magnetic Resonance Imaging
FoV	Field of View
FWE	Family-Wise Error
GR	Glucocorticoid Receptors
HCC	Hair Cortisol Concentration
HPA	Hypothalamus-Pituitary-Adrenal
HR	Heart Rate
iMAST	Imaging Maastricht Acute Stress Task
Inf.FG	Inferior Frontal Gyrus
ITI	Inter-Trial Interval
MDBF	Mehrdimensionaler Befindlichkeitsfragebogen
MIST	Montreal Imaging Stress Task

MNI	Montreal Neurological Institute
MR	Mineralocorticoid Receptors
MRI	Magnetic Resonance Imaging
mPFC	Medial Prefrontal Cortex
PASTOR	Positive Appraisal Style Theory of Resilience
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
rmANOVA	Analysis of Variance (repeated-measure)
ROI	Region of Interest
S1 – S6	Saliva Cortisol Samples 1-6
SAM	Self-Assessment Manikin
Scan*STRESS*-C	Scan*STRESS*-Compact
SECPT	Social-Evaluative Cold Pressure Task
SG	Stress Group
sgACC	Subgenual Anterior Cingulate Cortex
SMA	Supplementary Motor Area
SNS	Sympathetic Nervous System
SPM	Statistical Parametric Mapping
SRT	Script-based Reappraisal Task
Sup.FG	Superior Frontal Gyrus
TE	Echo Time
TSST	Trier Social Stress Test
TR	Repetition Time
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex

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Sandner, M., Lois, G., Streit, F., Zeier, P., Kirsch, P., Wüst, S., & Wessa, M. (2020). Investigating individual stress reactivity: High hair cortisol predicts lower acute stress responses. Psychoneuroendocrinology, e104660. https://doi.org/10.1016/j.psyneuen.2020.104660

List of Original Manuscripts

Sandner, M., Zeier, P., Lois, G., & Wessa, M. (2020). *Cognitive emotion regulation withstands the stress test: an fMRI study on the effect of acute stress on distraction and reappraisal* [Manuscript submitted for publication]. Institute of Psychology, Johannes Gutenberg University Mainz.

1 Introduction

1.1 Aim and Structure of the Dissertation

Stress is an inevitable part of our daily lives. From everyday hassles to longer-lasting challenging environments, we are surrounded by stressors throughout the lifespan. From an evolutionary perspective, stress in general constitutes an adaptive response to a threat or challenge by enhancing alertness and providing the resources to face and master the challenge. However, stress has become ubiquitous in modern life, both work and private, with significant effects on well-being and mental health. Nowadays, stress is commonly associated with the development and maintenance of psychiatric diseases, such as depression (Mazure & Maciejewski, 2003; Vogt, Waeldin, Hellhammer, & Meinlschmidt, 2016), anxiety disorder (Kara & Polo, 2014; Shin & Liberzon, 2010), and schizophrenia (Corcoran et al., 2003; Klippel et al., 2018), as well as higher risk of relapses in eating disorder or addiction (Milivojevic & Sinha, 2018; Pool & Sander, 2019; Sinha & Jastreboff, 2013). In addition, prolonged or chronic stress is commonly associated with a dysregulation of physiological processes and is considered a risk factor for various physical diseases such as cardiovascular diseases, osteoporosis or obesity (Brown, Varghese, & McEwen, 2004; Golbidi, Frisbee, & Laher, 2015; Kivimäki & Steptoe, 2018; Tomiyama, 2019). In this light, the importance to understand stress in all its complexity and with all its consequences has driven research of various disciplines for decades. The first aim of this dissertation was to complement this field of research by providing a sophisticated and holistic characterization of the dynamic stress response system with all its facets and influencing factors (Study 1). Therefore, we implemented and adapted an experimental paradigm to induce stress in a laboratory setting, the Scan*STRESS*-C, and proved its validity in eliciting multidimensional stress responses. In addition, we investigated the influence of long-term cortisol concentration on acute stress reactivity to evaluate the role of recent stress exposure in the context of stress resilience (for details, see Study 1).

Emotion regulation (ER) is one of the most prominent constructs in psychological research. The ability to deliberately regulate our emotional experience is of high relevance to adequate functioning in a social environment. Various mental disorders are associated with a deficit in ER, i.e. anxiety disorder, depression, and borderline personality disorder (Berking & Wupperman, 2012; Cludius, Mennin, & Ehring, 2020; Dryman & Heimberg, 2018; Kanske, Heissler, Schönfelder, & Wessa, 2012; Kanske, Schönfelder, Forneck, & Wessa, 2015). In reverse, successful ER has been linked to positive long-term mental health

outcomes (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Boyes, Hasking, & Martin, 2016; Sloan et al., 2017). However, the cognitive regulation of ER is a complex resource-intensive inner-psychological process involving multiple higher order executive functions such as attention, working memory, and cognitive flexibility (Hofmann, Schmeichel, & Baddeley, 2012; Ochsner, Silvers, & Buhle, 2012; Schmeichel, Volokhov, & Demaree, 2008). To date, it is yet unclear, if ER abilities may be impaired when probably needed the most: in the face of an acute stressor. This is of particular interest in resilience research, where cognitive ER is currently discussed as a possible resilience mechanism (Kalisch, Müller, & Tüscher, 2014). In this context, the second aim of this dissertation was to systematically investigate the effect of acute stress on subsequent ER in an fMRI (functional magnetic resonance imaging) setting (Study 2). In this regard, we intended to contribute to a better understanding of stress-related dysfunctions and -in the long run- to promote the development and improvement of prevention and intervention programmes in the context of stress resilience.

1.2 Acute Stress

1.2.1 Stress – Definition and Concepts

In psychological research, stress is conceptually defined as the result of an internal appraisal process: according to Lazarus and Folkman (1984), the feeling of stress is evolving if an individual is facing an acute challenge that is perceived to exceed the individual's coping abilities. This definition implies a complex inner-psychological appraisal process that is most certainly influenced by a variety of contextual and personal factors. Thus, stress is commonly considered a rather complex and multi-layered response to a perceived threat, which impairs biological homeostasis and comes along with an elaborate response pattern at multiple response levels, which will be described in detail below (McEwen, 2000). The holistic examination of these multiple stress responses as well as their interaction with higher-order psychological processes is of high importance given the decisive role of stress in the development and maintenance of various physical and mental diseases (Brown et al., 2004; Kara & Polo, 2014; Kivimäki & Steptoe, 2018; Pool & Sander, 2019).

1.2.2 Acute Stress Responses

Affective Stress Response

According to the Lazarus and Folkman definition, stress is occurring, if a challenge is perceived to exceed the individual's abilities to cope with it. Naturally, this comes along

with a temporal decline in psychological well-being. When assessing the subjective response to a laboratory stressor, participants frequently reported a significant increase of negative emotions, e.g. anxiety, sadness, anger, irritability, despair, or mental overload (e.g. Akdeniz et al., 2014; Dickerson & Kemeny, 2004; Lederbogen et al., 2011; Plessow, Kiesel & Kirschbaum, 2012; Selye, 1973; Smeets et al., 2012). These changes in emotional state can be transient or persisting, or even leading to stress-related depressive symptoms (Brown et al., 2004).

Endocrine Stress Response

On an endocrine level, stress is characterized by two prominent response systems: (1) the catecholaminergic system, and (2) the corticosteroid system. (1) Sympathetic nervous system (SNS) activity increases immediately after stress onset, triggering the release of catecholamines (i.e. adrenalin and noradrenalin) of the adrenal medulla. In the periphery, adrenalin and noradrenalin contribute decisively to the typical sympathetic bodily state of a *fight or flight* condition (see also chapter 2.3.4). In addition, stress immediately triggers the production of noradrenalin in the locus coeruleus in the brain. Here, noradrenergic effects differ between brain regions due to local differences in distribution and affinity of adrenergic receptors (see subsection 'Neural Stress Response').

(2) The corticosteroid system is a more prolonged and slower-acting endocrine stress response. The hypothalamus-pituitary-adrenal (HPA) axis constitutes a multi-stage cascade with first, corticotropin-releasing hormone (CRH) being produced in the paraventricular nucleus of the hypothalamus and released into the portal circulation system, where CRH then triggers the release of adrenocorticotropic hormone (ACTH) of the adenohypophysis. ACTH effects the production of corticosteroids, i.a. cortisol, in the adrenal cortex, which is then released to the blood stream, exerting various effects in the periphery (see subsection 'Psychophysiological Stress Response') and the brain (see subsection 'Neural Stress Response'). Cortisol as the end-product of this multistage HPA axis is known to be slowly increasing with a maximum in concentration 20-30 min after stress onset (Kirschbaum & Hellhammer, 1994). At an early stage, cortisol is interacting with catecholaminergic activity and potentiating the early effects on the brain and body. In addition, the lipophilic character of the cortisol-molecule allows it to pass the cell membrane, where it influences protein biosynthesis by modulating the gene expression rate in the long run. These inner-cellular genomic effects of cortisol can last from hours to days in the aftermath of a stressor.

Neural Stress Response

In the brain, both catecholamines as well as cortisol interact with multiple cortical and subcortical structures with regionally specific and sometimes opposite effects due to differences in receptor distribution and affinity. At moderate levels of catecholamine concentration, noradrenaline binds optimally to high-affinity α2A-receptors with high density in the prefrontal cortex (PFC), mediating executive control functions at no-stress conditions. At high levels of catecholamine concentration however, e.g. in the face of stress, low-affinity α1-receptors in the PFC and β1-receptors in the amygdala mediate a suppression of neuronal firing in the PFC and an increase in activity of i.a. the amygdala. This effect is further potentiated by the early non-genomic effects of cortisol, which is passing the blood-brain barrier and binding to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). High-affinity MR are mainly found in limbic structures such as the amygdala, increasing neuronal excitability here, while low-affinity GR are distributed in large parts of the brain, including the PFC, altering prefrontal functioning at high-levels of cortisol, i.e. stress.

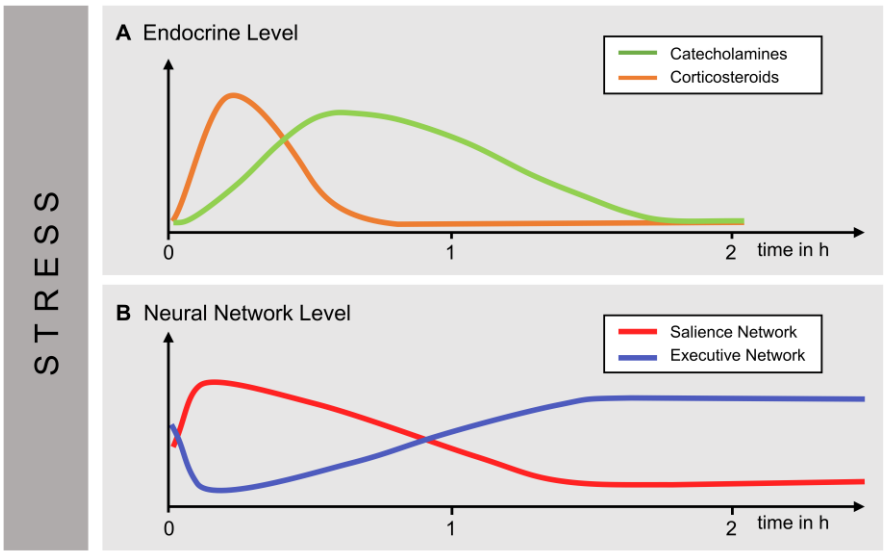

Figure 1. Biphasic model of systematic reallocation of neural resources in response to stress on (A) endocrine level and (B) neural network level, modified from Hermans et al. (2014).

To sum up, both endocrine stress systems interact and contribute to a strategic reallocation of cognitive resources in the face of acute stress. On this, Hermans, Henckens, Joëls, and Fernández (2014) postulated a model of intricately timed stress-related modulations of large-scale neural networks (see Figure 1) by integrating data of molecular, brain system and behavioral studies in rodents and humans. They delineate significant stress-related increases in activity and connectivity of regions associated with the *salience network*, namely the dorso-anterior cingulate cortex (dACC), the anterior insula, the amygdala, as well as regions in the striatum and the brainstem (Seeley et al., 2007). These salience network structures are known to be involved in processes of sensory attention, integration of interoceptive feedback, or threat detection (Dedovic, D'Aguiar, & Pruessner, 2009; Hermans et al., 2014; Phelps & LeDoux, 2005). Hence, their stress-related increase in activity and connectivity might contribute to a hypervigilant bodily state to enable rapid unpremeditated reactions to a changing environment or a potential threat in form of an acute stressor. In parallel, due to limited cognitive resources and triggered by the early neuroendocrine effects, activity in the *executive network* is downregulated during and shortly after acute stress, according to Hermans and colleagues (2014). This fronto-parietal network, involving dorsolateral and medial prefrontal regions, is usually associated with higher-order cognitive functions, such as working memory, cognitive flexibility, or response inhibition (Seeley et al., 2007). There is empirical evidence on stress-related impairments in executive functioning (Shields, Sazma, & Yonelinas, 2016), suggesting that acute stress is indeed limiting processing resources of the executive network for the sake of salience network functioning.

Importantly, about one hour after stress onset, this large-scale network pattern is proposed to switch: supported by genomic effects of cortisol, activity in the salience network is actively downregulated, while the executive network activity increases. This switch in network activity is postulated to contribute to a restoration of cognitive control mechanisms and executive functioning of the PFC when recovering from stress. To date, the model by Hermans and colleagues (2014) is empirically not fully confirmed yet, but it is considered a valuable attempt at a holistic perspective of the complex neuro-endocrine interplay in the face of stress.

Psychophysiological Stress Response

These dynamic neuroendocrine interactions orchestrate a complex psychophysiological stress response of the body. Catecholaminergic effects in the periphery

differ depending on receptor distribution, including immediate cardiovascular changes, i.e. increase in heart rate (HR) and blood pressure, as well as muscular contraction, peripheral vasoconstriction, and energy mobilization (Ulrich-Lai & Herman, 2009). In addition, circulating corticosteroids exert various metabolic effects, i.e. promoting the glucogenesis in the liver and inhibiting glucose absorption in muscles and fatty tissue, thereby contributing to the mobilization of stored energy and potentiating numerous sympathetic effects. Hence, these dynamic physiological changes aim at bringing the body to an ergotropic state (*fight or flight*) to ensure reflexive responsiveness and the ability to act when facing changing environments or an acute stressor.

1.2.3 Chronic Stress Conditions

While the acute stress response in all its complexity can be considered an adaptive response to a transient stressor, it is assumed that prolonged or frequent increases in HPA axis activity, as in chronically stressful environments, result in a persisting dysregulation of biological systems and constitute a risk factor for various physical and mental diseases (Miller et al., 2007; Stalder & Kirschbaum, 2012). Here, persisting or frequently elevated cortisol levels are discussed to cause hypersensitization of negative feedback mechanisms influencing receptor density and target tissue sensitivity at several stages of the HPA axis (Fries, Hesse, Hellhammer, & Hellhammer, 2005). In line with that, there is some evidence of long-term HPA axis alterations, both hyper- and hypocortisolism, in several psychiatric conditions, i.e. affective disorders, or posttraumatic stress disorder (Speer, Semple, Naumovski, D'Cunha, & McKune, 2019; Stetler & Miller, 2011).

Current research on long-term HPA axis alterations benefits from a recent methodological development: the analysis of cortisol concentration in hair. As cortisol is incorporated into the growing hair, analyzing the most proximal centimetres closest to the scalp offers a retrospective estimate of systemic cortisol exposure in the recent months. Although multifactorial in nature, hair cortisol concentration (HCC) is considered a valid biomarker of systemic cortisol exposure over longer periods of time (Stalder & Kirschbaum, 2012) and was used in Study 1 of this dissertation to investigate long-term HPA axis activity and its influence on acute stress reactivity measures. Note, that HCC is certainly influenced by a wide array of situational, socio-demographic and genetic factors (Dettenborn, Tietze, Kirschbaum, & Stalder, 2012; Rietschel et al., 2017; Staufenbiel, Penninx, de Rijke, van den Akker, & van Rossum, 2015). Nevertheless, HCC has become an increasingly popular instrument in chronic stress research, as multiple reviews and meta-analyses report

associations of HCC with recent or ongoing stress exposure in terms of unemployment, caregiving, or psychopathological condition (Russell, Koren, Rieder, & Van Uum, 2012; Stalder et al., 2017; Staufenbiel, Penninx, Spijker, Elzinga, & Van Rossum, 2013). HCC as an indicator of recent stress exposure will become relevant when discussing the results of Study 1 of this dissertation (see chapters 2.5 and 4.3).

1.3 Emotion Regulation

1.3.1 The Importance of Emotion and Emotion Regulation

From an evolutionary perspective, emotions in general constitute an adaptive response to threats to homeostasis or physical integrity. If our former ancestors were attacked by a tiger, the emotion fear or maybe anger may have been crucial for survival, providing the energy needed to fight the tiger or escape from it. It still holds true today: emotions significantly influence behavior, by playing a major role in the detection and satisfaction of basal needs. Motivated behavior is aimed at achieving positive emotions and avoiding negative ones. Emotional responses can thus be described as orchestrated multisystem reactions to motivationally relevant stimuli or situations (Moors, 2009). Hence, emotions in general have a huge motivational impact on our actions and our physical and mental health. But sometimes, if emotions are too intense, too prolonged, or poorly matched to the situational demands, these emotions can become dysfunctional. If for example one is experiencing overwhelming anxiety in the context of an oral exam, this anxiety is no longer a functional and adaptive response to the situational demands, but it is rather dysfunctional and counteracting goal-directed behavior. Hence the emotion in this case should be subject to regulation.

Emotion regulation is one of the most prominent constructs in psychology and psychotherapy. Decays of research investigated how to deal with dysfunctional emotional responses and their impact on behavior and health. Until now, it is proven that the ability to cognitively regulate emotions can improve resilience and prevent or alleviate psychological disorders (Berking & Wupperman, 2012; Cludius et al., 2020; Gross & John, 2003; Sloan et al., 2017). However, current research identifies various strategies to regulate different aspects of an emotional response. James Gross, one of the earliest and most prominent experts in the field of ER, made an attempt to structure the broad field of ER research by suggesting a process model of ER.

1.3.2 The Process Model by James Gross

The process model by James Gross (1998) suggests different stages in the generation of an emotion: When confronted with an aversive stimulus or situation, e.g. an oral exam, this situational input is processed within a "black box", i.a. the inner workings of the subject, possibly influenced by personality factors, e.g. shyness, and habitual response tendencies. At the end of this processing stage, there is the emotion as a result, e.g. fear or panic.

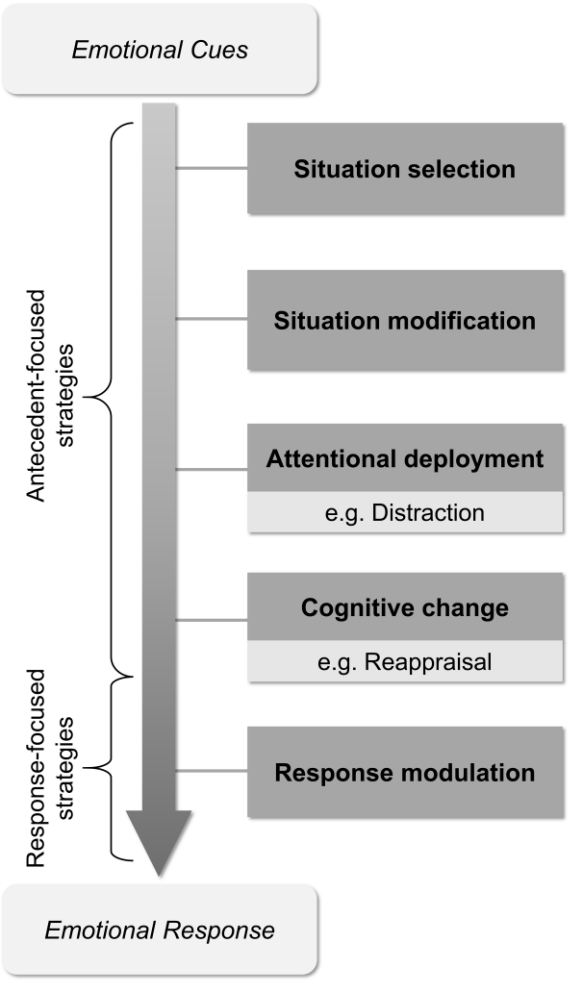

Figure 2. The process model of emotion regulation, modified from Gross (1998): Classification of ER strategies based on their chronological relevance in the process of emotion generation.

According to Gross (1998), there are different possibilities for the modification of this emotional output at the different stages of emotion generation (see Figure 2): there are either antecedent-focused strategies that aim at altering the emotional input into the whole system, or response-focused strategies targeting the output. To avoid (*situation selection*) or

modify (*situation modification*) aversive situations, e.g. the oral exam, would most certainly change or dampen the emotional output but may not be the most adequate and goal-directed response in the long run. On the other side, *response modulation* also constitutes an adaptive way to cope when already in the emotion, e.g. breathing technique to alleviate exam anxiety. However, it requires high levels of self-reflection and self-regulation. Hence, previous research identified *distraction* (as an attentional deployment strategy) and *reappraisal* (as a cognitive change strategy) to be the most efficient and most applicable ER strategies (Webb, Miles, & Sheeran, 2012).

1.3.3 Cognitive Reappraisal and Distraction

Distraction incorporates the redirection of attention away from emotion-triggering stimuli, e.g. focusing on the characteristics of the room or one's own notes instead of symptoms of fear arising or the strict face of the examination board members. *Reappraisal* involves a re-interpretation of the given situation with the aim to alter its emotional impact, e.g. interpreting the oral exam as a great opportunity to show what has been learned. Both strategies proved to efficiently regulate emotional states on different outcome levels. On a subjective rating level, distraction and reappraisal were associated with a decrease in negative emotions and an increase in psychological well-being (Gross & John, 2003; Song et al., 2019; Wu et al., 2019). On a peripher-physiological level, both strategies resulted in changes in heart rate variability (Denson, Grisham, & Moulds, 2011), startle responses (Dillon & LaBar, 2005; Ray, McRae, Ochsner, & Gross, 2010) and facial electromyography (EMG) (Ray et al., 2010). And on a neural level, decreased activity in regions associated with affective processing, i.e. the amygdala, was reported to go along with both distraction and reappraisal (Buhle et al., 2014; Ochsner et al., 2012). Moreover, studies directly comparing neural networks during distraction and reappraisal report a large overlap of both strategy-specific brain activations (Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011): Both strategies recruit a large network of ventrolateral and dorsolateral prefrontal as well as parietal parts of the cortex (Buhle et al., 2014; Morawetz, Bode, Derntl, & Heekeren, 2017). Connectivity studies suggest that these regions exert a top-down regulation on limbic structures, thereby contributing decisively to the regulation of emotional responses (Kanske et al., 2011).

In addition, previous research suggests differences in the regulation success of the two strategies according to contextual factors of the emotional situation. Studies on ER choice for example indicate that when given the choice, distraction is chosen over

reappraisal when the emotion is highly intense (Shafir, Thiruchselvam, Suri, Gross, & Sheppes, 2016; Sheppes & Levin, 2013; Sheppes et al., 2014). This is in line with other studies suggesting that cognitive reappraisal can be considered a complex interplay of multiple executive functions, such as attention, working memory, and cognitive flexibility (Hofmann et al., 2012; Ochsner et al., 2012; Schmeichel et al., 2008), which, if successful, results in a persisting change of emotional states, while at the same time requiring a decent amount of cognitive resources (see chapter 1.4). Hence, while both being effective, reappraisal results in long-lasting effects and highest effect sizes when dealing with moderate intense emotions whereas distraction might be more robust to contextual demands, such as situations with high emotional intensity, e.g. in the face of stress (McRae & Gross, 2020; Webb et al., 2012).

1.4 Emotion Regulation in the Face of Acute Stress

As mentioned earlier, the cognitive regulation of emotional states is a prominent construct in psychological research. There is a multitude of previous studies investigating the underlying cognitive mechanisms and influencing factors. Within these studies, there are indices of cognitive ER failing in stressful circumstances, following two major explanatory approaches: Stress may affect ER by A) increasing overall emotional reactivity, or B) by depriving resources from brain regions known to be critical to successful ER.

A) Acute stress was previously reported to increase general emotional sensitivity (Alomari, Fernandez, Banks, Acosta, & Tartar, 2015; van Marle, Hermans, Qin, & Fernandez, 2009; Weymar, Schwabe, Löw, & Hamm, 2012). As described earlier, the sympathetic response to an acute stressor triggered by catecholaminergic and salience network activity (see chapter 1.2.2) contributes to a hypervigilant state of environment scanning and threat detection. Hence, sensitivity for emotionally relevant stimuli is enhanced in the face of stress as well as the intensity of the emotional experience (Weymar et al., 2012). Importantly, other studies on ER indicate, that the higher the emotional intensity, the greater the amount of cognitive resources required, the harder to regulate these high-intense emotions (Shafir, Schwartz, Blechert, & Sheppes, 2015; Silvers, Weber, Wager, & Ochsner, 2015). Apparently, especially cognitive reappraisal is a strategy less applied and less effective when dealing with high intense emotions (Murphy & Young, 2018; Opitz, Cavanagh, & Urry, 2015; Shafir et al., 2016; Sheppes, Scheibe, Suri, & Gross, 2011). Hence,

acute stress may impair cognitive ER capacities by increasing sensitivity to and intensity of emotional cues.

B) In addition, acute stress was reported to be associated with increases in salience network activity, as described in chapter 1.2.2. At the same time, neural activity in the prefrontal regions of the executive control network is decreased during or immediately after acute stress (see also Figure 1 and Hermans et al., 2014). Since ER is known to rely heavily on prefrontal functioning (Buhle et al., 2014), it is assumed, that this strategic reallocation of cognitive resources may contribute to impairments in ER capacities. In this line, stress has been shown to impair those executive functions relevant for cognitive reappraisal, such as cognitive flexibility (Plessow, Fischer, Kirschbaum, & Goschke, 2011) and working memory (Shields et al., 2016). To date it is yet unclear, whether and to what extent stress indeed affects ER and whether the explanatory approach A), or B), or a combination of both can be accounted as the underlying mechanism.

Only a few experimental studies so far directly investigated cognitive ER strategies in the context of stress. Raio, Orederu, Palazzolo, Shurick, and Phelps (2013) trained their participants in using cognitive ER strategies to deal with a fear conditioning paradigm. They discovered that when previously confronted with an acute laboratory stressor, participants failed at using these newly acquired ER skills to reduce their fear responses to the conditioned aversive stimulus. Hence, in this study, acute stress undermined the effect of the ER training on fear conditioned stimuli. In parallel, Zhan et al. (2017) reported previously stressed participants to be less effective in using cognitive reappraisal to reduce anger, compared to participants of a control group. Kinner, Het, and Wolf (2014) investigated the distinct effect of an acute laboratory stressor on different ER strategies. They specifically assessed two components of emotional responding: the valence dimension (ranging from ‘pleasant’ to ‘unpleasant’) as well as the arousal dimension (‘calm’ to ‘excited’), using Self-Assessment Manikin (SAM) scales (Bradley & Lang, 1994). The authors discovered that distraction, but not reappraisal, was impaired in the stress group, as indicated by higher arousal ratings of stressed participants. Interestingly, reappraisal ability was even enhanced after stress, but only in female participants and only in valence, not arousal ratings. Hence, these results suggest that acute stress may influence different emotion regulation strategies specifically for valence and arousal, and that this influence may differ according to sex. In this line, Langer et al. (2020) recently published their result of a stress-related enhancement in cognitive ER (i.e. reduced arousal and more positive valence ratings), but only in male participants. In a recent fMRI study, Shermohammed et al. (2017) investigated the effect of

an acute psychosocial stressor on the neural underpinnings of cognitive reappraisal. Interestingly, in their study, the stress and the control group did not differ, neither in emotional reactivity, nor in reappraisal success and neither in subjective valence ratings, nor in ER-related brain activity. Hence, a clear direct effect of acute stress on ER could not be detected in this fMRI study where the stress task and the ER paradigm were interleaved. Recent data of our own laboratory (Rimpel et al., not published) indicates that the timing of the experimental tasks might play an important role in the context of stress and ER: we found an impairment in cognitive reappraisal in the stress group compared to the control group, in an ER paradigm that took place 40-60 min after stress induction. Notably, no such stress effect on cognitive reappraisal was observed in an earlier phase 20-40 min after the stressor, indicating the effect of stress on ER might depend on the experimental timing. In this line, Jentsch, Merz, and Wolf (2019), instead of using laboratory stress induction, administered 30 mg external cortisol or a placebo at about 90 min prior to the ER paradigm. Interestingly, they reported an enhancement in ER abilities in the cortisol group compared to the placebo group. Although real-life or laboratory stressors differ remarkably from the mere administration of external cortisol, Jentsch et al. (2019) provide first evidence for a cortisol-induced facilitation of ER in the aftermath of a stressful event (see Figure 1 and Hermans et al., 2014). Hence, the effect of acute stress on cognitive ER might underlie a distinctive timely pattern mirroring the fine-tuned temporal dynamics of the neuroendocrine stress response (see chapter 1.2.2).

1.5 Conclusion and Research Questions

To conclude, while there are indices for a stress effect on ER, it is yet unclear, whether, to what extent, and under which circumstances acute stress affects which cognitive ER strategy. However, answering these questions is of particular interest in resilience research, where cognitive reappraisal, as an inherent part of a general positive appraisal style, is currently discussed to be a key mechanism of resilience (Kalisch et al., 2014, see also chapter 4.3). The ability to successfully regulate emotional states is believed to buffer the negative effects of adverse life events or trauma. Hence, in a bidirectional relationship, ER may also buffer the negative effects of stress on psychological wellbeing (see chapter 1.2.2). However, if ER is impaired when facing an acute threat or challenge, recovery from or resilience to acute stress exposure might be limited. In this light, disentangling this complex bidirectional relationship of stress and ER might be of high relevance for the

prevention or intervention of stress-related physical and mental diseases. This dissertation aims at contributing to this systematic investigation by providing an experimental stress protocol, which is both, intense enough to elicit multidimensional stress responses in the fMRI laboratory as well as short enough to investigate subsequent ER abilities in the aftermath of this stressor. In the following, the implementation and validation of this experimental stress paradigm (Scan*STRESS*-C) is further described (Study 1). Specifically, we investigated the influence of long-term HPA axis activity on multidimensional stress reactivity. The Scan*STRESS*-C was then furthermore applied in Study 2 to systematically investigate the effect of the multidimensional stress response on subsequent ER.

2 Study 1: Investigating Individual Stress Reactivity: Higher Hair Cortisol Predicts Lower Acute Stress Responses [1]

[1] Publication Reference: Sandner, M., [redacted], G., [redacted], F., [redacted], P., [redacted], P., [redacted], S., & [redacted], M. (2020). Investigating individual stress reactivity: High hair cortisol predicts lower acute stress responses. Psychoneuroendocrinology, e104660. https://doi.org/10.1016/j.psyneuen.2020.104660

2.1 Summary of Study 1

Identifying individual differences in stress reactivity is of particular interest in the context of stress-related disorders and resilience. Previous studies already identified several factors mediating the individual stress response of the hypothalamus–pituitary–adrenal axis (HPA). However, the impact of long-term HPA axis activity on acute stress reactivity remains inconclusive.

To investigate associations between long-term HPA axis variation and individual acute stress reactivity, we tested 40 healthy volunteers for affective, endocrine, physiological, and neural reactions to a modified, compact version of the established in-MR stress paradigm Scan*STRESS* (Scan*STRESS*-C). Hair cortisol concentrations (HCC) served as an integrative marker of long-term HPA axis activity.

First, the Scan*STRESS*-C version proved to be valid in evoking a subjective, endocrine, physiological, and neural stress response with enhanced self-reported negative affect and cortisol levels, increased heart rate as well as increased activation in the anterior insula and the dorso-anterior cingulate cortex (dACC). Second and interestingly, results indicated a lower neuroendocrine stress response in individuals with higher HCC: HCC was negatively correlated with the area under the curve (respect to increase; AUCi) of saliva cortisol and with a stress-related increase in dACC activity.

The present study explicitly targeted the relationship between HCC and acute stress reactivity on multiple response levels, i.e. subjective, endocrine and neural stress responses. The lower stress reactivity in individuals with higher HCC levels indicates the need for further research evaluating the role of long-term HPA axis alterations in the context of vulnerability or immunization against acute stress and following stress-related impairments.

2.2 Introduction

Although individuals differ remarkably in their physiological and psychological reaction to an acute stressor, the identification of factors contributing to these individual differences in stress reactivity is of particular interest in the context of stress-related disorders and resilience.

Acute stress is associated with complex reactions on different bodily dimensions. On an affective level, stress is the result of an appraisal process when situations are evaluated as threatening and overwhelming based on the available coping resources (Lazarus & Folkman, 1984). Hence, a decrease in psychological well-being is frequently reported by individuals confronted with stressful stimuli (Elling et al., 2012; Plessow et al., 2011). On an endocrine level, stress regulation is characterized by a two-component response system. Immediately after stress onset, activation of the sympathetic nervous system triggers the production of catecholamines in the adrenal medulla (De Kloet, Joels, & Holsboer, 2005). In parallel, activity of the slower-acting hypothalamus-pituitary-adrenal (HPA) axis increases. As a consequence of a multistage cascade, a rise in corticosteroids, i.e. cortisol, can be observed by analyzing saliva samples with a peak at about 20-30 minutes after the onset of a typical laboratory stress paradigm (e.g., Trier Social Stress Test (TSST); Kirschbaum et al., 1993). On a neural level, catecholamines and corticosteroids, interact with cortical and subcortical structures, contributing to a strategic resource reallocation in the face of acute stress. Regions associated with the salience network, e.g. the anterior insula, the dorso-anterior cingulate cortex (dACC), and the amygdala (Seeley et al., 2007), show increased activity following stressful events, whereas the prefrontal cortex shows decreased activity in stressful conditions (Hermans et al., 2011). These dynamic neuroendocrine interactions orchestrate a complex psychophysiological response to stress (Hermans et al., 2014) to enable rapid and adequate reactions to a changing environment. In addition to these rapid endocrine stress effects, cortisol exerts inner-cellular genomic effects due to its lipophilic character, lasting from hours to days or even months after acute stress exposure (Joëls & Baram, 2009). Given these complex reactions to an acute stressor, a multidimensional stress assessment is required when investigating individual stress reactivity in an experimental setting.

Previous studies already identified several factors influencing the individual HPA axis reaction to an acute stressor, e.g. age, gender, body mass index (BMI) and smoking behavior (Kudielka, Hellhammer, & Wüst, 2009; Zänkert, Bellingrath, Wüst, & Kudielka, 2018). However, another factor potentially influencing acute stress reactivity is an alteration

in long-term HPA axis activity. While the acute and transient increase in cortisol concentration can be considered an adaptive response to a challenge, prolonged or frequent increases in HPA axis activity are associated with various maladaptive effects (Chrousos, 2009), contributing to a persisting dysregulation of biological stress systems (Stalder & Kirschbaum, 2012). Therefore, the exploration of long-term HPA axis activity as a potential factor contributing to inter-individual differences in acute stress reactivity is an important research aim.

In the current study, we aimed at investigating the potential influence of HPA axis functioning on acute stress reactivity, using a biomarker of long-term HPA axis activity. The analysis of cortisol concentration in hair (HCC) is a recent methodological development providing a valid and objective measure of systemic cortisol exposure over longer periods of time (Russell et al., 2012; Stalder et al., 2017; Staufenbiel et al., 2013). As cortisol is incorporated into the growing hair, the analysis of HCC offers a retrospective assessment of cortisol production within the last few months. This long-term HPA axis marker is positively correlated with total saliva cortisol output cumulated over multiple day assessment (van Holland, Frings-Dresen, & Sluiter, 2012; Xie et al., 2011; Zhang et al., 2018) or with the cortisol awakening response (Vanaelst et al., 2012; see Stalder et al., 2017 for a review). However, only few studies investigated HCC and saliva cortisol in the context of acute stress reactivity, yielding inconclusive results. For example, one study in soldiers showed a trend-wise positive correlation between HCC and the cortisol response to acute stress (Steudte-Schmiedgen et al., 2015), while another study in patients with depression and/or anxiety was lacking significant correlations (Steudte-Schmiedgen et al., 2017). To date, studies in healthy individuals are scarce, although this sample proves beneficial when avoiding disease-related confounds in long-term HPA axis activity. As a first study, Bendezù and Wadsworth (2017) focused on a sample of preadolescents exposed to the TSST. The authors report a significant increase in saliva cortisol after the TSST, yet this cortisol increase was not differentially associated with either self-reported stressful life events or HCC levels. Another study reported no significant correlations of HCC with saliva cortisol increase during a physical activity intervention (Grass et al., 2015). In summary, studies explicitly targeting the relationship between HCC and multidimensional measures of acute stress reactivity are lacking so far.

Thus, the aim of the current study was two-fold: First, we set out to investigate acute stress reactivity on an affective, endocrine, heart rate, and neural level. To induce a stress response, we used an adapted version of an already established valid stress paradigm carried

out in the scanner, the Scan*STRESS* (Akdeniz et al., 2014; Dahm et al., 2017; Lederbogen et al., 2011; Streit et al., 2014). Adaptations included shortening the paradigm and grouping control blocks and stress blocks into two different experimental phases. We thereby intended to establish a paradigm, allowing the investigation of time-dependent acute stress effects on subsequent neurocognitive processes in future studies (see chapter 2.3.3 for details). According to previous studies on acute stress responses (Joëls & Baram, 2009; Kirschbaum et al., 1993; Plessow et al., 2011), we hypothesized a stress-related decrease in affective well-being from pre- to post-stress as well as increases in saliva cortisol concentration and heart rate. On a neural level, we expect the anterior Insula and the dACC, as core structures of the salience network, as well as the supplementary motor area (SMA) and the amygdala to be more active during stress than during control blocks, according to previous results (Streit et al., 2014). As a second study aim, we hypothesized that long-term HPA axis activity, as assessed by HCC, explains individual differences in acute stress reactivity on the measured response levels. However, considering the scarce and ambiguous evidence from previous studies, this hypothesis was non-directional.

2.3 Methods

2.3.1 Participants

Forty participants (12 women; 36 right-handed) at the age of 19 to 32 years (M = 24.93, SD = 3.79) were recruited for participation via flyer and postings at the campuses of university and university medical center Mainz, Germany. All participants were extensively screened via telephone, reporting in the negative with respect to acute or chronic diseases, history of mental disorders, past or ongoing psychotherapy treatment, history of neurological, cardiovascular, or endocrine diseases, use of steroid-based lotions or asthma sprays, and smoking behavior or use of opioids or cannabis. We excluded participants with a BMI (kg/m²) below 18 and over 26. An additional inclusion criterion for female participants was the intake of oral contraceptives to reduce variability in cortisol responses related to hormonal alterations throughout the menstrual cycle phase. The study was approved by the local ethics committee of the Psychological Institute of the Johannes Gutenberg University Mainz according to the declaration of Helsinki. All participants gave written and informed consent and received 60 Euros for their participation.

2.3.2 Procedure

The experimental procedure lasted approx. 2.5 hours. Upon arrival, participants were provided with information on the study aim and procedure. To ensure the authenticity of the experimental stress paradigm, we provided a cover story informing participants of the alleged study aim, i.e. an investigation of neural activity patterns in performance situations. Participants subsequently completed questionnaires on the state of their well-being as well as a training session of the MRI-tasks. Afterwards, they watched a relaxing movie for approximately 30 min to minimize baseline differences in cortisol concentration. Thereafter, participants entered the MR scanner. For details on the MRI session see chapter 2.3.4, details of the Scan*STRESS*-C procedure are explained in chapter 2.3.3. After participants left the scanner, they again indicated their current emotional state and were debriefed in detail. During the experiment, we collected six saliva samples to ensure frequent monitoring of changes in cortisol concentrations (see chapter 2.3.4 for details).

2.3.3 The compact Scan*STRESS* (Scan*STRESS*-C)

The experimental stress protocol adopted in this study was originally developed at the Central Institute of Mental Health in Mannheim and described in detail in Streit et al. (2014). Like the original Scan*STRESS*, Scan*STRESS*-C consists of a stress and a control condition, implemented in Presentation® software (Version 19.0, www.neurobs.com). During stress blocks, participants performed two types of cognitive challenging tasks (mental rotation and arithmetic subtraction, see Figure 1-1) under time pressure while lying in the MR scanner. Task speed and difficulty were adapted to the individual's performance by way of an algorithm, thereby forcing failure. Social-evaluative elements were added by transmitting a video livestream of a jury in lab coats continuously displaying disapproving facial feedback. In case of slow or incorrect answers, the jury gave negative feedback in terms of short written instructions (e.g. "Work faster!") via a red buzzer. To further increase stress effects, the jury provided standardized negative verbal feedback via speakers in the middle of the stress phase; for this purpose, the scanner was briefly stopped after three blocks of stress tasks. During the verbal feedback, participants were reminded that *"showing maximum effort is of crucial importance for the sake of sufficient data quality*" and that *"the performance so far was below average*". In the control blocks, participants had to perform simple figure- and number-matching tasks (without rotation or subtraction) in the absence of time-pressure and negative feedback. Here, participants were also shown the video-livestream of the jury, which in this case remained passive and did not observe the

participants' behavior or look into the camera. In addition, the video picture was overlaid by a grey diagonal cross to signal the absence of active monitoring, see Figure 1-1.

In the current study, the stimuli of the stress induction and control task did not differ from the original Scan*STRESS*. Further, Scan*STRESS*-C also uses a block design. However, two adaptations were made regarding the timing and sequence of the blocks: (1) we shortened the block duration from 60 to 40 sec with a 20 sec rest period separating the blocks. (2) We rearranged the sequence of control and stress blocks to form two separate, non-randomized experimental phases, i.e. a first control phase and a subsequent stress phase, each consisting of six blocks of control or stress tasks, respectively (see Figure 1-1). We aimed at modeling a naturalistic, brief, and distinct stress exposure, uninterrupted by artificial non-stress phases, as is the case in the original alternating block design from Streit et al. (2014). Thus, like established laboratory stress protocols outside the scanner (e.g., TSST), the Scan*STRESS*-C offers a more compact and in-MR option to investigate time-dependent stress effects for example on subsequent psychological processes. Therefore, we named it compact Scan*STRESS* (Scan*STRESS*-C). For a further discussion of the pros and cons of Scan*STRESS* and Scan*STRESS*-C see chapter 2.5.

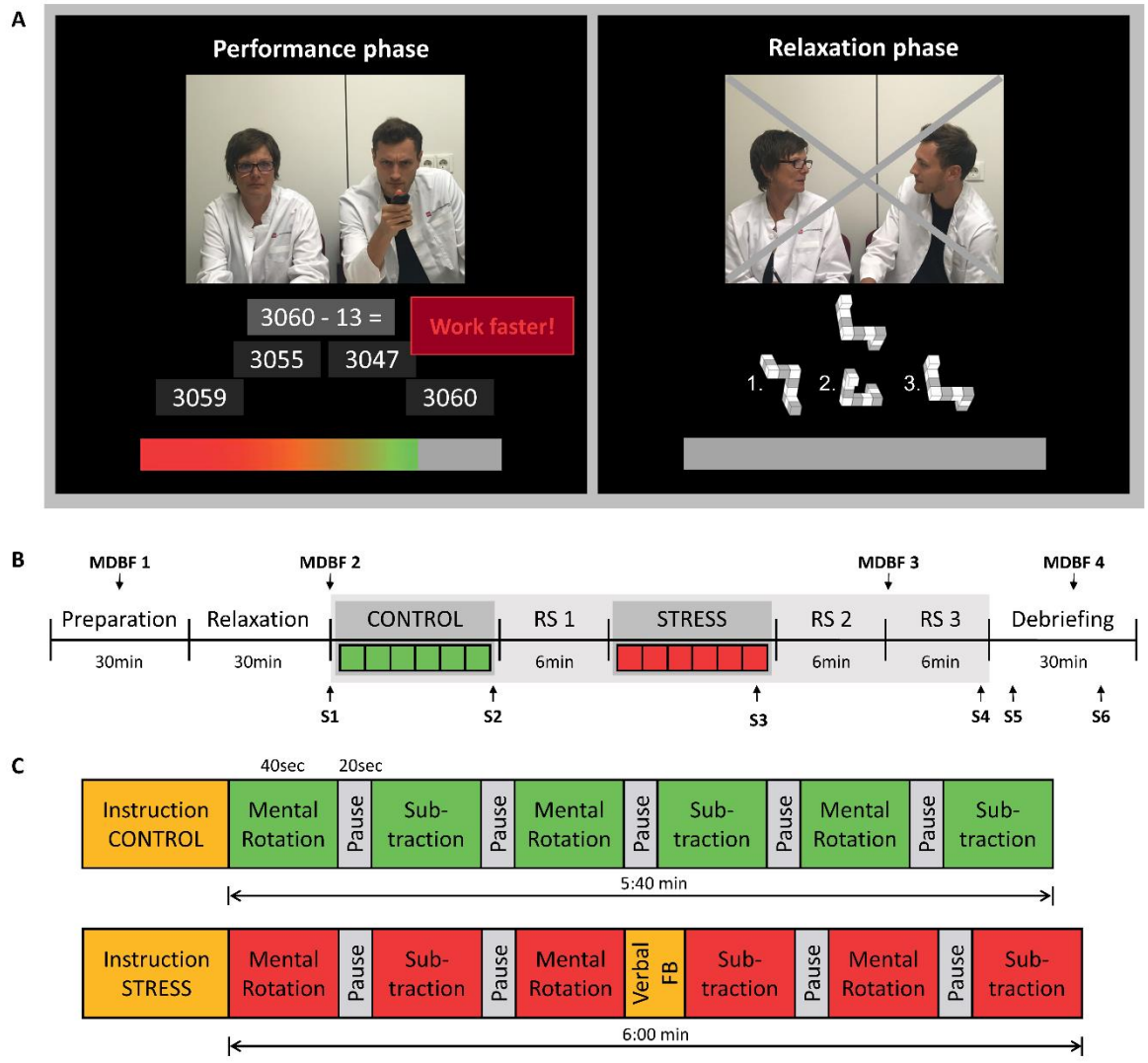

Figure 1-1. Overview of experimental procedure. (A) Different tasks of the Scan*STRESS*-compact (Scan*STRESS*-C), mental rotation and subtraction task, presented in the performance and the relaxation phase of the stress paradigm. The countdown bar indicates the remaining time to process the particular task. (B) Schematic of the complete experimental session, including the MRI part (light gray) and the Scan*STRESS*-C (dark grey), as well as saliva sampling and MDBF rating. (C) Details on the control (relaxation) and the stress (performance) phase. FB = feedback; MDBF = German Mood Questionnaire; RS1-RS3 = resting state measures; S1-S6 = saliva cortisol samples.

2.3.4 Markers of Acute Stress Reactivity

Affective Stress Reactivity

To investigate stress responses on a self-reported affective level, we used the German mood questionnaire "Mehrdimensionaler Befindlichkeitsfragebogen" (MDBF, Steyer et al., 1997). The MDBF includes a list of adjectives reflecting positive or negative emotional states. The participants' ratings on a five-point Likert scale can be summed up to a total score of subjective well-being. Higher scores reflect a more positive, lower scores a more negative emotional state. In this study, participants rated their subjective well-being four times during the experiment (see Figure 1-1). In-MR assessments were carried out using an MR-compatible response pad (NAtA Technologies®, LxPad, Coquitlam, Canada). Sufficient reliability (Cronbach's alpha $\alpha = .80$ to .92) and validity of the MDBF was confirmed in several studies (Buckert, Schwieren, Kudielka, & Fiebach, 2014; Klinkenberg et al., 2016; Plessow et al., 2011). In the present study, Cronbach's alpha of $\alpha = .93$ indicated excellent internal consistency.

Endocrine Stress Reactivity

Cortisol concentrations prior to and in response to the Scan*STRESS*-C were obtained with Salivette® devices (Sarstedt AG & Co, Nümbrecht, Germany). In total, participants provided six saliva samples during the experiment to ensure frequent monitoring of changes in cortisol concentration (see Figure 1-1). In-MR samples were taken by moving the bench outside the scanner only far enough for the experimenter to place a Salivette in the participants' mouth for two minutes, but the bench was never removed from the scanner completely. This procedure allowed for (a) keeping the position in the head coil and the reference coordinates of each scan unchanged with respect to the anatomical MRI and thereby (b) avoiding repeated localizers (see Dedovic et al., 2005 for details on the in-MR sampling procedure). All saliva samples were stored at -20°C and sent to the Institute of Biopsychology at the Technical University Dresden, Germany, for analysis. Salivary concentrations were measured using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients were below 8%.

Heart Rate Stress Reactivity

Heart rate (HR) changes during the Scan*STRESS*-C protocol were recorded with an MR-compatible pulse-oximeter with an infrared emitter placed under the pad of the left index finger (50 Hz sampling).

fMRI Acquisition and Analysis

Imaging data was acquired on a 3T scanner (Siemens Trio, Erlangen, Germany) with a 32-channel head coil. The following parameters were used for anatomical pictures: slice thickness = 1 mm; FoV = 250 mm; voxel size: 1 mm isotropic; TR = 1900 ms; TE = 2.52 ms; flip angle = 9°. Functional pictures during the Scan*STRESS*-C were acquired using identical echo planar imaging (EPI) multiband sequences with the following scanning-parameters: slice thickness = 2.5 mm; FoV = 210 mm; voxel size: 2.5 mm isotropic; TR = 1000 ms; TE = 29 ms; flip angle = 56°; multiband acceleration factor = 4. The complete MRI session included three resting state sequences, which are beyond the scope of this paper. Preprocessing and statistical analysis were conducted using Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm). We discarded the first four images of each sequence to account for inhomogeneities of the magnetic field. Images were realigned to the first functional image by a 6-parameter rigid body transformation, then co-registered to the anatomical T1 scan, transformed to the Montreal Neurological Institute (MNI) EPI reference space (voxel size: 3 mm isotropic) and smoothed with an 8 mm full-width at half-maximum Gaussian filter. Individual subjects' data were analyzed within a general linear model framework. In the first level analysis, we included one control regressor modelling the onsets and duration of the 40 sec active control task blocks, and two stress regressors modelling the onsets and duration of the 40 sec active stress task blocks. Two stress regressors were included as the stress phase was split into two sequences due to the verbal feedback. The two stress regressors were combined to be compared to the no-stress control regressor. The 40 sec active control task and active stress task blocks were interleaved with 20 sec pauses, which served as an implicit baseline. In addition, six motion regressors were included as covariates of no interest to control for residual motion artefacts after reorientation. For further analyses, we excluded two participants with a movement of 2 mm or more between volumes. For details on the first level design matrix, see Supplement Figure SF1-1. We computed contrast images of stress versus control condition for each participant to investigate the general effect of task (stress induction). The t-contrast images obtained were subjected to second-level models, using a one-sample *t*-test to test the general effect of

acute stress. For the main task effects (stress vs. control and control vs. stress), imaging results were corrected via family-wise error (FWE) for multiple comparisons at a significance level of $p_{whole\_brain} < .05$. Peak voxels are reported and labelled according to the Automated Anatomical Labelling (AAL) atlas by Tzourio-Mazoyer et al. (2002) (see Table 1-2).

To analyze the relationship between hair cortisol levels and Blood-oxygen-level-dependent (BOLD) responses during acute stress, we extracted the mean subject-specific *z*-values of significant clusters from the main effect contrast 'stress vs. control' using the MarsBaR toolbox (http://marsbar.sourceforge.net). Specifically, we focused on the anterior insula and the dACC as core structures of the salience network.

2.3.5 Marker of Long-Term HPA Axis Activity

The concentration of cortisol in hair served as an integrative marker of long-term HPA axis activity. Hair samples were obtained by separating hair from the vertex posterior region of the participant's head into a strand of 1 cm^3 in diameter and 3 cm in length (~7,5 mg) and cutting it as close to the scalp as possible. Hair samples were stored at room temperature without light exposure and sent to the Institute of Biopsychology at the Technical University Dresden, Germany, for an analysis of cortisol concentrations according to the protocol of Davenport et al. (2006) (chemiluminescence immunoassay, CLIA, IBL-Hamburg, Germany, intra- and interassay coefficient of variance below 8%). As hair grows approx. 1 cm per month, the analysis of the most proximal 3 cm of the strand provided information about systemic cortisol exposure over the last three months preceding the experiment.

2.3.6 Statistical Analyses of Stress Reactivity and HCC Data

Statistical analysis of affective, endocrine, and heart rate data was carried out using SPSS 22 (SPSS Inc., Chicago, IL, USA). For all analyses of variance (ANOVAs), which will be described below, statistical effects were evaluated using the Greenhouse–Geisser correction when appropriate.

Affective Data Analyses

First, MDBF sum scores were computed according to the manual (Steyer et al., 1997), ranging from 1 to 15, with higher scores indicating higher subjective well-being. To indicate affective stress reactivity, we computed the difference in self-reported well-being

pre- to post-stress (MDBF2-MDBF3). To investigate stress-related changes in affective state, we conducted a repeated-measure ANOVA (rmANOVA) with "time" (4 levels) as a within-subject factor. Post-hoc analyses of contrast focused on pre-stress (MDBF2) and post-stress scores (MDBF3).

Endocrine Data Analyses

Cortisol data was logarithmized to base 10 in order to reduce typical data skewness. We computed the area under the curve with respect to increase (AUCi; Pruessner et al., 2003) in saliva cortisol for each participant separately to index total cortisol reactivity to the stressor. In addition, other widely used cortisol measures were computed to account for alternative strategies of cortisol analyses, i.e. individual baseline-to-peak values, cortisol responses (as the difference between S5 +32 min and S2 -6 min, relative to stress onset), and cortisol recovery (as the difference between S6 +65 min and S5 +32 min). Data are presented in Supplement 1-2.

To examine temporal fluctuations in concentration following the stressor, we conducted an rmANOVA with "time" (6 levels) as within-subject factor. Post-hoc analyses of contrast focused on the samples immediately before (S1 -20 min, S2 -6 min) and after (S3 +6 min, S4 +22 min) the stress protocol. As cortisol responses to acute stress have been shown in some studies to be sensitive to sex effects, we repeated the rmANOVA with sex as between-subject factor, see Supplement 1-3 for details.

Heart Rate Data Analyses

For each subject, the average heart rate was computed for the control and the stress phase separately. A paired *t*-test compared both mean values in heart rate. In addition, the difference between both values quantified individual stress-induced increases in heart rate.

Correlational Analyses

To test our hypothesis of alterations in acute stress reactivity due to long-term HPA axis activity, subsequent Pearson's bivariate correlation analyses were performed. For this purpose, we correlated HCC with our measures of stress reactivity: 1) AUCi cortisol increase, 2) stress-related heart rate changes, 3) stress-related BOLD-responses in brain regions of the salience network resulting significant from the 'stress vs. control' contrast, i.e. the dACC (3a), and the anterior insula left (3b) and right (3c) (see Supplement 1-6 for complementary information on exploratory correlational analyses with significant activations

and deactivations other than those of the salience network), and 4) stress related changes in affective well-being (MDBF2-MDBF3, see Figure 1-1). Bonferroni correction was applied to correct for multiple testing, see chapter 2.4.2.

To further examine neuro-endocrine intercorrelations in response to acute stress on an exploratory level, we correlated individual cortisol baseline-to-peak increase with stress-related neural activity in significant regions of the salience network.

2.4 Results

2.4.1 Validation of Scan*STRESS*-C

To check for successful stress induction by the Scan*STRESS*-C, we analyzed stress-related changes in subjective well-being, saliva cortisol concentrations, heart rate, and BOLD-responses. See Supplement Table ST1-1 for descriptive statistics of all stress reactivity markers as well as a detailed correlational matrix, including both inter-correlations between reactivity markers and correlations with HCC.

Affective Stress Response

On an affective level, MDBF data from two participants were missing and excluded. The MDBF means and standard deviations are listed in Table 1-1. A significant main effect of "time" indicated that mean MDBF levels differed significantly between measurements, $F(3, 111) = 13.48$, $p < .001$, partial $\eta^2 = .27$ (Greenhouse-Geisser corrected, $\varepsilon = .80$), see Figure 1-2B. Post-hoc contrasts revealed a significant difference between MDBF scores before (MDBF2, $M = 11.69$, $SD = 1.72$) and after (MDBF3, $M = 10.57$, $SD = 1.97$) the stress task, $F(1, 37) = 22.47$, $p < .001$, indicating more negative mood ratings at MDBF3.

Endocrine Stress Response

For endocrine analyses, we excluded two participants due to missing cortisol values. Mean cortisol concentrations at the respective time points are depicted in Table 1-1. The rmANOVA revealed a significant main effect of "time", $F(5, 185) = 18.59$, $p < .001$, partial $\eta^2 = .33$ (Greenhouse-Geisser corrected for lacking sphericity, $\varepsilon = .44$), indicating a statistically significant difference in cortisol concentration before (S2) and approximately 22 min (S4) after stress induction, $F(1, 37) = 49.56$, $p < .001$, partial $\eta^2 = .57$ (see Figure 1-2A and Table 1-1 for means and standard deviations). Classification of cortisol responders based on a baseline-to-peak increase of > 1.5 nmol/l (Miller et al., 2013) resulted

in a responder rate of 73.7 %. Note that cortisol responders and non-responders did not differ in any of the other reactivity markers, see Supplement 1-4. We observed no sex effects on stress-related cortisol responses (see Supplement 1-3 for details).

Table 1-1
Means (standard deviations) of neuroendocrine and subjective data.

	Sampling Time relative to stress onset	**Cortisol** in nmol/l
S1	-20 min	4.35 (3.15)
S2	-06 min	5.07 (3.46)
S3	+06 min	5.78 (3.76)
S4	+22 min	7.99 (5.38)
S5	+32 min	8.46 (7.29)
S6	+65 min	6.52 (5.57)
	Assessment Time (relative to stress onset)	**MDBF** Sum Score
MDBF 1	-75 min	11.86 (1.70)
MDBF 2	-18 min	11.69 (1.72)
MDBF 3	+16 min	10.57 (1.97)
MDBF 4	+40 min	11.51 (1.99)

Note. MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol samples.

Heart Rate Stress Response

For heart rate analyses, we had to exclude eight participants due to recording issues. Figure 1-2C depicts the time course of the heart rate during the control (M = 74.84, SD = 20.44) and stress phase (M = 84.93, SD = 14.75). A paired t-test confirmed a significant increase in heart rate during the stress phase, $t(31) = 33.12$, $p < .001$, $d = .85$.

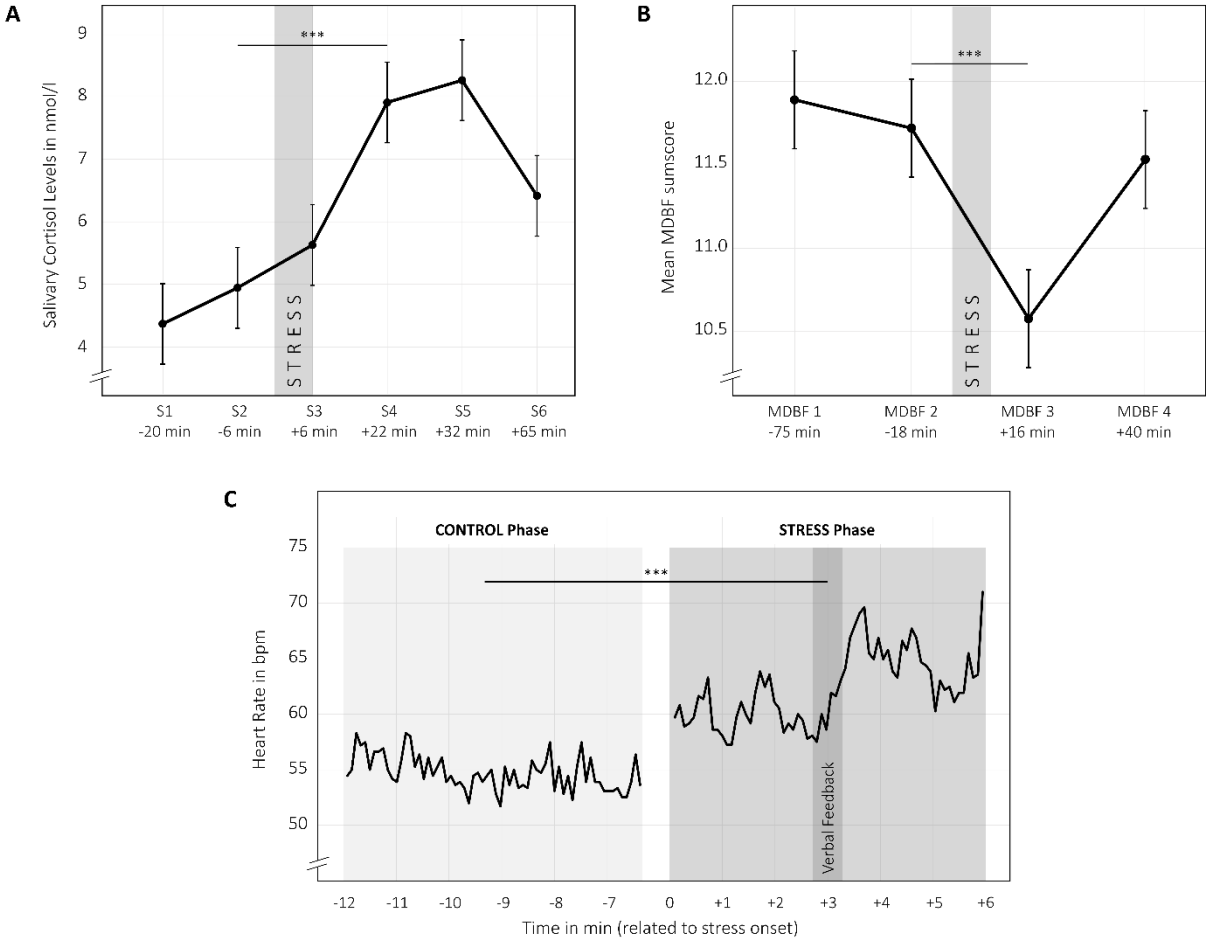

Figure 1-2. Acute stress reactivity on multiple response levels. Saliva cortisol levels (A) and mood ratings (B) at respective time points, as well as heart rate values (C) during the control and the stress phase of the Scan*STRESS*-C. MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol levels (untransformed).
*** $p < .001$.

Neural Stress Response

For MRI analyses, we excluded two participants due to insufficient data quality caused by head movements (at least one movement between volumes exceeding 2 mm; see chapter 2.3.4 for details). Figure 1-3 illustrates activations and deactivation in response to the stress vs. control phase. Contrasting neural activity during the stress vs. control phase revealed significant activation increases in structures of the salience network, i.e. the bilateral anterior insular cortices, the dACC, the SMA, and the brainstem (all ps < .001, whole-brain FWE-corrected, Figure 1-3). Further significant activations were found in the parietal and occipital cortex and the cerebellum (see Table 1-2 for further details on

significant local maxima with MNI coordinates). We furthermore found significant stress-related deactivations in medial regions of the prefrontal cortex, temporal regions, bilaterally in the amygdala as well as the cerebellum (see Table 1-2 for details).

To examine neuro-endocrine interactions in response to stress, we correlated saliva cortisol AUCi with stress-related brain activity in structures of the salience network. Results show a significant correlation of cortisol AUCi with dACC activity, $r(36) = .38$, $p = .024$, but not with activity in the anterior insula left, $r(36) = .12$, $p = .503$, or right, $r(36) = .22$, $p = .207$. See Supplement 1-2 for correlational analyses of neural clusters and additional cortisol markers, e.g. recovery.

Table 1-2

MNI coordinates of peak voxels and corresponding T and $p_{\_FWE}$ values of activation clusters that show significant activation or deactivation

Brain structure		**MNI coordinates**			**Statistical values**		
		x	y	z	*k*	Mean *T*	$p_{\_FWE}$
Activation (stress versus control)							
Anterior insula cortex	L	-32	20	0	340	12.92	< .001
	R	32	24	-2	399	12.83	< .001
Inferior parietal cortex	R	44	-40	46	4226	12.68	< .001
	L	-42	-42	48	3754	11.17	< .001
Superior frontal gyrus	R	26	4	62	1480	11.43	< .001
	L	-22	4	56	598	10.62	< .001
Inferior frontal gyrus (pars opercularis)	L	-44	10	30	652	10.64	< .001
	R	46	10	28	461	10.60	< .001
Inferior temporal gyrus	R	54	-50	-10	139	9.40	< .001
Cerebellum	M	-4	-72	-24	572	9.13	< .001
	R	22	-70	-44	112	8.26	< .001
	L	-32	-70	-48	86	7.64	< .001
Inferior frontal gyrus (pars triangularis)	R	46	32	20	338	8.18	< .001
	L	-38	24	24	152	7.63	< .001
Brainstem	M	-8	-26	-12	158	8.09	< .001
Dorsoanterior cingulate cortex	M	-2	6	24	23	7.51	< .001
Fusiform gyrus	L	-32	-56	-16	26	6.82	< .001
Middel occipital gyrus	L	-10	-94	-2	16	6.75	< .001
Deactivation (control versus stress)							
Medial frontal gyrus	L	-14	44	44	2006	11.44	< .001
Posterior cingulate cortex	M	-2	-44	30	1135	9.42	< .001
Angular Gyrus	L	-50	-70	36	400	9.32	< .001
	R	58	-60	34	134	8.10	< .001
Rolandic operculum	R	42	-14	18	65	7.80	< .001
	L	-38	-16	20	23	6.94	< .001

Cerebellum	R	30	-84	-36	96	7.71	< .001
Amygdala	R	22	4	-6	58	7.32	< .001
	L	-24	-2	-8	13	6.84	.001
Precentral gyrus	R	18	-30	68	48	7.17	< .001
Temporal Mid	R	58	-2	-26	66	7.04	< .001
	L	-60	-10	-16	23	6.47	< .001

Note. L = left hemisphere; R = right hemisphere; M = medial; *k* = cluster size in voxels; MNI = Montreal Neurological Institute.

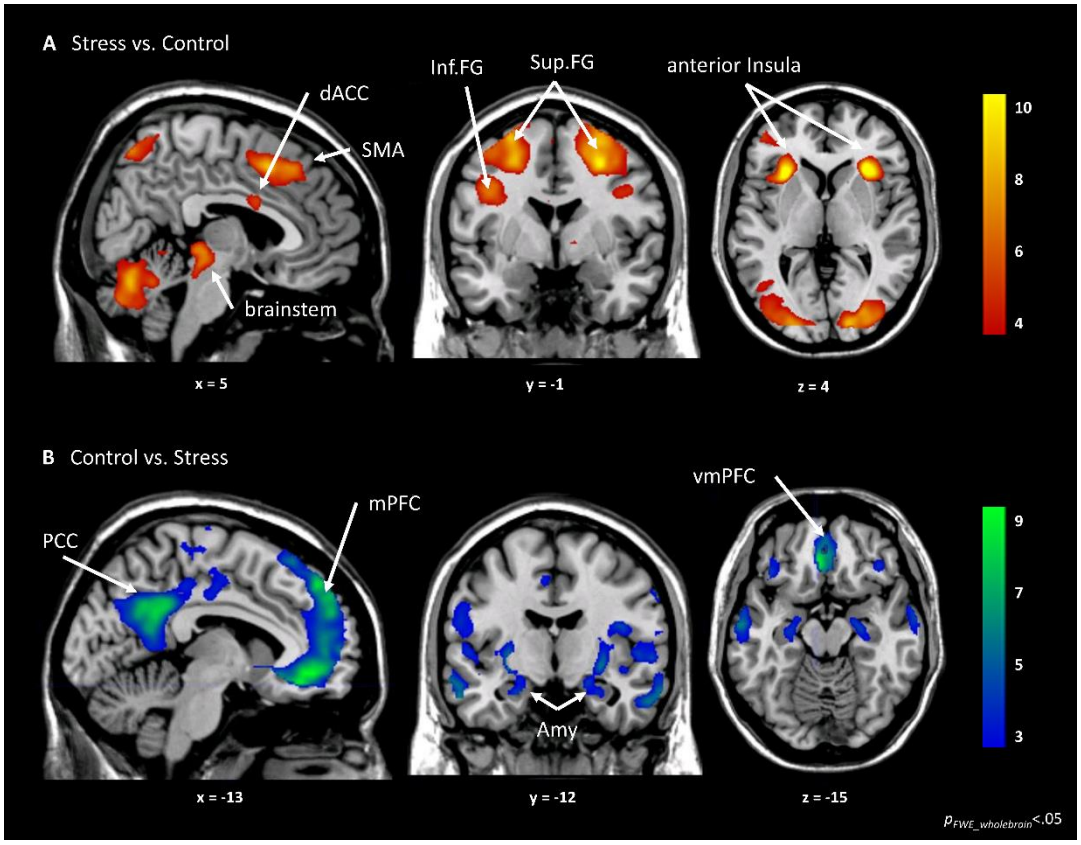

Figure 1-3. Main effect of social stress induction: activation (A) and deactivation (B). Neural response included activations in i.e. anterior insula cortex, dorso-anterior cingulate cortex, supplementary motor cortex, and brainstem and deactivations in i.e. medial frontal gyrus, posterior cingulate cortex, and amygdala (all $p < .05$, whole-brain FWE corrected). For graphical display, MRIcroN (https://www.nitrc.org/projects/mricron) was used with the MNI template brain. Amy = amygdala; dACC = dorso-anterior cingulate cortex; FEW = family-wise error corrected for multiple comparisons; Inf.FG = inferior frontal gyrus; MNI = Montreal Neurological Institute; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; Sup.FG = superior frontal gyrus; vmPFC = ventromedial prefrontal cortex.

2.4.2 Relationship between Long-Term HPA Axis Activity and Acute Stress reactivity

For six participants, hair sampling was impossible due to insufficient hair length. Correlational analyses were restricted to the intersection of participants for whom data on most stress reactivity markers (i.e. AUCi-, HR-, and BOLD-responses) were available, resulting in $n = 31$ (case-wise procedure). Correlational analyses with heart rate were done in a subsample of $n = 26$ due to high missing rates in heart rate acquisition (see chapter 2.4.1 for details). Note that results did not change remarkably when analyses were performed on the largest sample size possible for each reactivity marker separately (pair-wise procedure), see Supplement 1-5. No statistical outliers (+/- 3 *SD* from *M*) had to be excluded from correlational analyses. Please note that according to the Bonferroni correction for multiple testing, correlations were considered significant when passing the following adjusted $p_{corr} < (.05/6) = .008$.

HCC correlated significantly negatively with the AUCi of saliva cortisol concentration, $r(31) = -.47$, $p = .007$ (see Figure 1-4A). Analyses in additional markers of cortisol reactivity or recovery confirmed the result (see Supplement 1-2). In addition, we observed a significant negative correlation between HCC and dACC activity, $r(31) = -.51$, $p = .003$ (see Figure 1-4B). We found a negative correlation of HCC with the left anterior insula that did not reach statistical significance, $r(31) = -.35$, $p = .053$. We observed no significant correlation of HCC and individual stress-related increase in HR or the right anterior insula (all *p*s > .10). HCC did not correlate significantly with the MDBF difference score, $r(31) = -.31$, $p = .095$ (see Figure 1-4C). For complementary information on other cluster correlations, see Supplement 1-6).

Since contraceptive medication is known to influence HCC as well as acute cortisol reactivity (Stalder et al., 2017) we ran several checks for sex effects in HCC and stress-induced cortisol levels as well as their relationship, yielding no significant effects (details in Supplement 1-3).

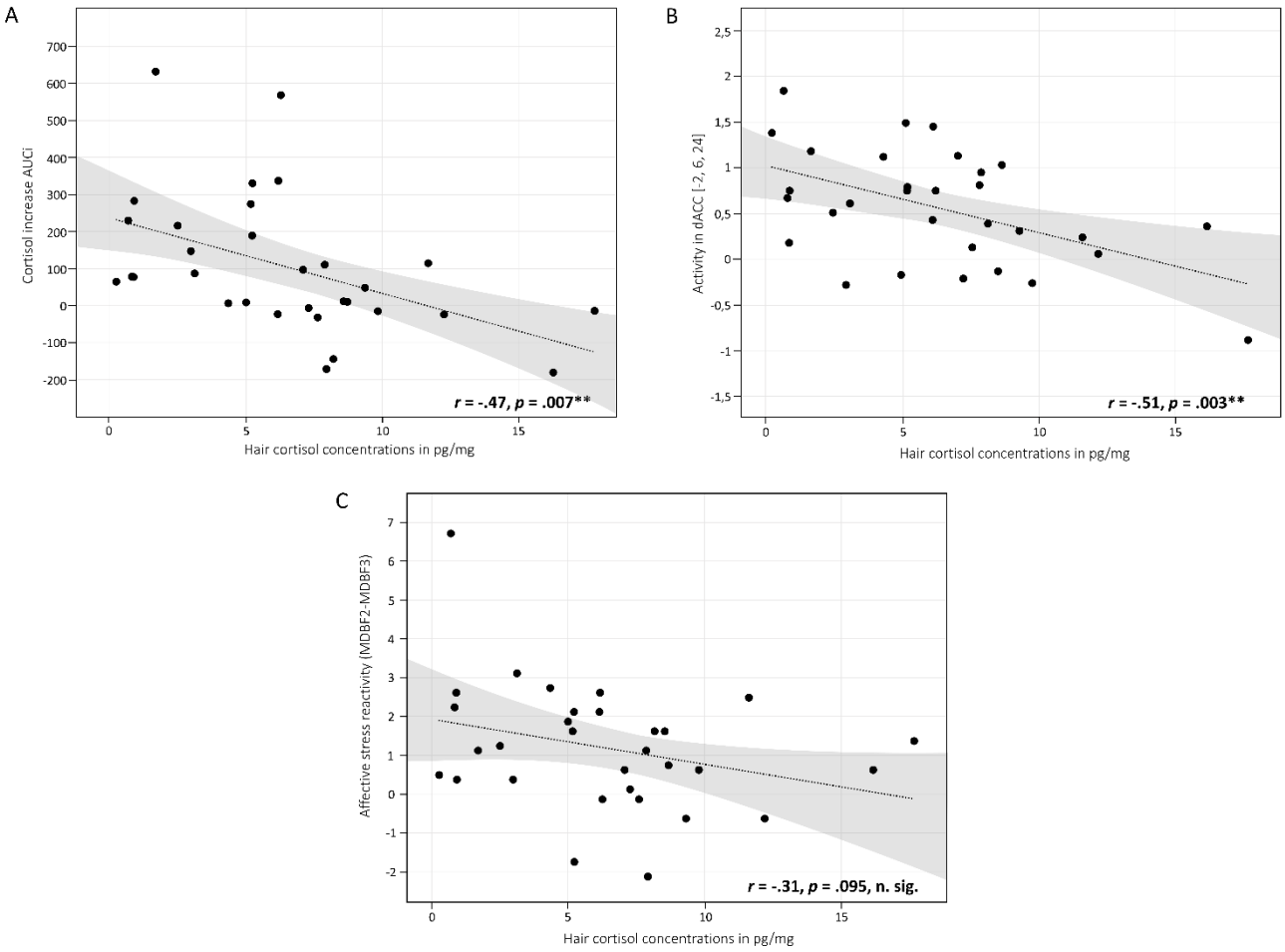

Figure 1-4. Results of correlation analyses. HCC correlates significantly with both, (A) stress–related cortisol increase, AUCi, as well as (B) stress-related activity in the dACC. Correlation of HCC and (C) affective stress response (MDBF2-MDBF3) was negative, but not significant. AUCi = Area under the curve with respect to increase; dACC = dorso-anterior cingulate cortex; HCC = Hair cortisol concentration; MDBF = German Mood Questionnaire. ** $p < .01$.

2.5 Discussion

The present study implemented and validated a modified, compact in-MR stress protocol (Scan*STRESS*-C) and examined the impact of long-term HPA axis activity on individual stress reactivity to this MRI stress protocol. Our findings are twofold: First, the adapted in-MR stress protocol (Scan*STRESS*-C) proved to be valid as shown by significant stress responses on affective, endocrine, physiological, as well as neural level. Second, individual neural and endocrine stress reactivity was negatively correlated with long-term cortisol production as indicated by HCC.

Validation and Discussion of ScanSTRESS-C

Regarding our first study aim, the validation of the Scan*STRESS*-C, we investigated acute stress responses to this experimental stressor on multiple response levels. The reported decrease in subjective well-being as well as the increase in saliva cortisol and heart rate to the Scan*STRESS*-C is consistent with a broad range of studies on acute social stress effects (Buckert et al., 2014; Lederbogen et al., 2011; Streit et al., 2014). Moreover, the responder rate of almost 74% stands up to comparison with the original Scan*STRESS* version (Streit et al., 2014) as well as other established and valid in-MR paradigms, e.g. the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) or the imaging Maastricht Acute Stress Task (iMAST; Quaedflieg et al., 2013). In line with previous studies, analyses of neural activity revealed significant stress-related activation in the anterior insula, the dACC, the SMA, and the brainstem. The dACC, for example, has been implicated in conflict monitoring, decision making and the experiences of social rejection or negative evaluation (Dedovic, Slavich, Muscatell, Irwin, & Eisenberger, 2016; Eisenberger, Lieberman, & Williams, 2003; Heilbronner & Hayden, 2016) which, in the present study, might indicate the increase in cognitive demands and social evaluation during the stress phase compared to the control phase. In addition, an increased functional connectivity between the dACC and cortical as well as subcortical structures, i.e. amygdala, was previously reported during acute stress (Hermans et al., 2011; van Marle, Hermans, Qin, & Fernández, 2010) as well as dACC connectivity changes during early recovery, that differed depending on cortisol responsiveness with reduced dACC-amygdala connectivity in responders only (Quaedflieg et al., 2015). Thus, the dACC shows dynamic connectivity changes in response to stress, contributing to the autonomic regulation of visceral-motoric as well as neuroendocrine responses to acute stress. Consequently, associations of stress-related dACC activity with changes in blood pressure and heart rate or saliva cortisol were found in previous studies

(Gianaros et al., 2008; Wager et al., 2009; Wang et al., 2007). Although we did not observe significant correlations with heart rate, our study confirmed the positive association between dACC activity and saliva cortisol to acute stress (see Supplement Table ST1-1).

In contrast to previous studies, we found the amygdala to be deactivated during stress, which is contrary to previous findings (Akdeniz et al., 2014; Dahm et al., 2017; Streit et al., 2014). One potential explanation may originate from methodological specifications of the Scan*STRESS*-C. We used a fixed-block design for the Scan*STRESS*-C instead of the alternated and inter-individually randomized block design in the original version, as we aimed at modelling a naturalistic and brief stress exposure (see chapter 2.3.3 for details). This missing randomization, however, bears the risk of order and time-dependent effects, e.g. fatigue of the participant or MRI signal-drift effects, influencing results when contrasting both phases. In this context, the adaptations to the experimental design may explain our finding of a stress-related amygdala deactivation, since transient anxiety-effects due to the scanner environment could result in stronger amygdala activation during the initial control phase compared to the subsequent stress phase. This potential systematic timing effect due to the control blocks in the beginning of the experiment is prevented in the original Scan*STRESS* by the alternating sequence of control and stress blocks. Despite these methodological limitations of the Scan*STRESS*-C, the present study has proven its validity in eliciting a significant stress response on the affective, endocrine, physiological, and neural level. Thus, the advantages and disadvantages of both the original Scan*STRESS* as well as Scan*STRESS*-C must be evaluated in light of study aims. When compared directly, we would suggest using the original Scan*STRESS* when investigating the neural correlates of stress induction *per se*. However, when the research aim includes the investigation of neural stress effects together with stress-induced neural changes in other psychological processes (e.g., decision-making, emotion regulation), the Scan*STRESS*-C in its shorter and intense design offers a valid alternative to the original Scan*STRESS*.

HCC Predicts Lower Neuro-Endocrine Stress-Reactivity

As a second, yet important finding of our study, we observed that endocrine and neural acute stress responses to the Scan*STRESS*-C procedure were negatively correlated to HCC, whereas affective and heart rate responses were not. This result can be explained and interpreted in several ways.

First, the restriction of our results to only saliva cortisol AUCi and dACC correlating with HCC suggests a biological explanation. HCC, as one integrative marker of long-term

HPA axis activity, is highly influenced by a wide array of situational, socio-demographic, and genetic factors (Rietschel et al., 2017), contributing to individual differences in general HPA axis activity. In general, variations in the HPA axis regulation are known to influence both HCC and acute saliva cortisol metrics, as shown in the context of physical activity (Skoluda, Dettenborn, Stalder, & Kirschbaum, 2012; Ullmann et al., 2016) or obesity (Papafotiou et al., 2017; see Rodriguez et al., 2015 for a review). It is assumed that an increased negative feedback mechanism as well as the downregulation of target tissue sensitivity and receptor density at several stages of the HPA axis may result in alterations in basal cortisol levels as well as cortisol reactivity (Fries et al., 2005). Hence, natural variations in HCC could explain variance in acute cortisol reactivity since both can be considered end products of the same underlying physiological system, the HPA axis. However, this explanation does not include the correlation of HCC with activation in the dACC during stress, which might rather be a result of sympathetic nervous system activation than the slower HPA axis response, since brain activity was recorded directly during the stress task and cortisol peaked approx. 22 min after stress onset.

Thus, a second approach may be considered to explain and interpret the present findings: reduced acute stress reactivity might be a result of recent stress experiences. The concentration of cortisol in hair, although multifactorial in nature, is also considered a valid estimate of the average cortisol output during the last three months. Multiple reviews and a recent meta-analysis report reliable and valid associations of HCC with recent or ongoing stress exposure in terms of e.g. unemployment, caregiving or psychopathological conditions (Herane-Vives et al., 2015; Russell et al., 2012; Stalder et al., 2017; Staufenbiel et al., 2013). Interestingly, Lam and colleagues (2018) investigated the relationship of acute stress reactivity and cumulative stress exposure, i.e. the total sum of all stressors experienced over the entire lifespan. Here, greater cumulative stress exposure was a significant predictor of blunted cortisol responses. In addition, adverse events in early life lead to reduced reactivity to acute stressors (Elzinga et al., 2008; Voellmin et al., 2015; see Fogelman & Canli, 2018 for a review).

Thus, exposure to mildly stressful events in the recent past may facilitate adaptive functioning when confronted with acute stressors by strengthening the body's regulatory systems and promoting the development of elaborate coping strategies. On the other hand, missing or blunted cortisol responses might also be maladaptive, as cortisol is an important component of the complex psychophysiological processes in the presence of an acute stressor, enabling rapid and adequate reactions to a changing environment (Hermans et al.,

2014). As in our study, we did not assess early life stress or chronic stress and daily hassles in a detailed manner, future studies are needed to systematically investigate the protective or maladaptive psychological and biological mechanisms underlying the relationship between HCC levels and acute stress reactivity in larger and more heterogeneous samples.

Limitations

Although our results provide valuable psychoneuroendocrinological insights in individual alterations in acute stress reactivity based on HCC variations, some methodological limitations need to be considered.

First, as mentioned before, the mere exposure to the scanner environment might have an effect on the participant's stress levels. In addition, even though unintended, the control task itself could also be experienced as stressful to some extent. This is especially relevant when interpreting MDBF data. Unfortunately, as we did not assess subjective well-being after the control phase, reflecting a pre-stress baseline level, we cannot disentangle whether and to what extent changes in subjective well-being at MDBF3 are influenced by either environmental effects or the control phase.

Second, as described in chapter 2.4.2., missing data from several participants in each stress reactivity measure resulted in n = 31 participants, for whom data on most stress reactivity markers were available. Although unfortunate, we believe that this rather high missing rate is a risk to take for the sake of a multilevel assessment of the complex processes following acute stress exposure. Nevertheless, generalizability of our results is limited. Future studies in larger samples are warranted to confirm the correlational findings and complement them.

Third, as mentioned before, unfortunately, we did not assess recent or chronic stress exposure on a self-report level. Future studies should consider including an assessment of daily hassles, chronic stress experiences as well as critical life events. Additionally, we screened for physical or mental diseases (see chapter 2.3.1) as exclusion criteria, resulting in a relatively healthy, well-educated, young sample. Further studies are warranted to investigate the relationship of HCC and acute stress-reactivity in samples of a broader age range, chronic stress experiences and/or (sub-) clinical symptoms or higher risk to develop mental disorders.

2.6 Conclusion

In conclusion, our findings suggest lower reactivity to an acute stressor in individuals with higher HCC. Further, the Scan*STRESS*-C proved to be a valid and time-economic tool to investigate the neural underpinnings of acute stress as well as its effects on psychological processes in future studies. This is the first study to report associations of acute stress reactivity at the endocrine and neural level with HCC. It therefore highlights the importance of long-term HPA axis alterations as a significant factor contributing to individual differences in acute stress-reactivity. Future studies will have to examine the protective or maladaptive psychological and biological mechanisms underlying the relationship between HCC levels and acute stress reactivity in larger and more heterogeneous samples.

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3 Study 2: Cognitive Emotion Regulation Withstands the Stress Test: An fMRI Study on the Effect of Acute Stress on Distraction and Reappraisal [2]

[2] Publication Reference: Sandner, M., [redacted], P., [redacted], G., & [redacted], M. (2020). *Cognitive emotion regulation withstands the stress test: an fMRI study on the effect of acute stress on distraction and reappraisal* [Manuscript submitted for publication]. Institute of Psychology, Johannes Gutenberg University Mainz.

3.1 Summary of Study 2

Cognitive emotion regulation is a key mechanism for the maintenance of mental health but may fail when individuals are exposed to acute stress. To date, it is not well understood whether and to what extent acute stress effects contribute to impairments in emotion regulation capacities as the sparse existing studies have yielded heterogeneous results. When systematically investigating emotion regulation in the face of stress, we expected significant effects of an acute laboratory stressor on a subsequent emotion regulation task.

In the present study, 81 healthy participants underwent either an acute stress task (Scan*STRESS*-C; $n = 40$) or a control condition ($n = 41$) while lying in the MRI scanner. In the subsequent Cognitive Emotion Regulation Task (CERT), participants were confronted with neutral or negative pictures and instructed to either view them, or regulate their upcoming emotions using either attentional distraction or situational reappraisal. Subjective ratings of affective state as well as functional brain imaging data served to indicate emotion regulation.

The results showed a successful stress manipulation as indicated by group differences in subjective wellbeing, heart rate, saliva cortisol concentrations, and functional brain activity in regions implicated in stress processing. With respect to emotion regulation, CERT data revealed a significant regulation effect at the neural and behavioral level (less negative emotional ratings after reappraisal and distraction trials compared to view trials) in both groups. However, no significant group differences were observed, indicating no stress-related impairments in different forms of cognitive emotion regulation.

Contrary to previous studies, we did not find stress-related effects on emotion regulation, potentially being related to differences between studies in experimental setting, timing, and procedures. This study therefore underlines the need of future studies that disentangle the complex interplay of stress and emotion regulation and identify different factors influencing their bidirectional relationship.

3.2 Introduction

The ability to deliberately regulate our emotions is of crucial importance to adequate psychosocial functioning and the maintenance of mental health, especially when facing acute stressors in life (McRae & Gross, 2020). However, little is known about how emotion regulation abilities change in acute stress situations, where these abilities are probably needed the most.

In general, cognitive emotion regulation constitutes an effective way to cope with emotions that are either too intense, or poorly matched to situational demands. In the last decades, a growing body of research identified and investigated different strategies of emotion regulation ranging from attentional deployment to cognitive change (Gross, 1998; Webb et al., 2012). Attentional deployment involves the redirection of attention away from emotion-triggering information (*distraction*). Cognitive change incorporates the *reappraisal* of a given stimulus or situation with the aim to change its emotional impact. Both strategies proved effective in altering emotions on multiple response levels: self-reported affective state (Song et al., 2019; Webb et al., 2012; Wu et al., 2019), peripheral physiological markers (Denson et al., 2011; Ray et al., 2010; Schönfelder, Kanske, Heissler, & Wessa, 2014), and neural measures of emotions (Kanske et al., 2011; Morawetz et al., 2017; Ochsner et al., 2012; Shahane, Lopez, & Denny, 2019). In general, successful emotion regulation has often been linked to long-term mental health outcomes (Aldao et al., 2010; Boyes et al., 2016; Cludius et al., 2020). Reversely, a deficit in cognitive emotion regulation is common to various mental disorders, i.e. anxiety disorder, depression, and borderline personality disorder (Berking & Wupperman, 2012; Joormann & Gotlib, 2010; Kanske et al., 2012, 2015) and is often the subject of cognitive behavioral therapy. Importantly, the cognitive regulation of emotions can be considered a complex interplay of multiple higher-order cognitive functions, such as attention, cognitive flexibility, and working memory (Hofmann et al., 2012; Ochsner et al., 2012; Papousek et al., 2017). Results from previous imaging studies indicate that emotion regulation relies heavily on prefrontal functioning, recruiting a network of ventrolateral (vlPFC) and dorsolateral (dlPFC) prefrontal and parietal regions usually implicated in cognitive control processes (Buhle et al., 2014). Connectivity studies suggest that these prefrontal regions exert a top-down regulation on limbic structures, i.e. the amygdala, thereby contributing decisively to the regulation of emotional responses (Buhle et al., 2014; Kanske et al., 2011).

Given the crucial role of prefrontal brain structures in cognitive emotion regulation, the effective implementation of the respective strategies may well be challenged in the face of acute stress as the secretion of stress hormones leads to activation changes in cortical and subcortical brain structures (Arnsten, 2009). More precisely, acute stress leads to an immediate increase in (nor)adrenalin triggered by the sympathetic nervous system, followed by a slower increase in cortisol, as an end-product of the multistage HPA cascade (De Kloet et al., 2005). These neuroendocrine interactions contribute to a systematic re-allocation of cognitive resources in the face of acute stress (Hermans et al., 2014): thus, activity increases in structures of the salience network, i.e. the anterior insula and the dorso-anterior cingulate cortex (dACC), to enhance alertness and enable the organism to react rapidly and adequately to a changing environment (Seeley et al., 2007). In parallel, mediated by the neuroendocrine substrates, acute stress is usually associated with diminished activity in higher-order prefrontal structures (Arnsten, 2009), possibly limiting higher order cognitive functioning. A second burden to emotion regulation under stress may refer to the stress-related increase of emotional sensitivity and intensity (van Marle et al., 2009; Weymar et al., 2012), which particularly impedes the implementation of emotion regulation strategies (Murphy & Young, 2018; Shafir et al., 2015; Webb et al., 2012).

In line with these considerations, previous studies investigating the relationship of acute stress exposure and emotion regulation reported a stress-related impairment in the cognitive regulation of previously fear-conditioned stimuli (Raio et al., 2013). Zhan et al. (2017) found reappraisal to be less effective in reducing anger in participants that have previously been stressed, compared to a control group. Kinner and colleagues (2014) explicitly targeted different emotion regulation strategies following an acute stress task and reported significant stress-related impairments in distraction, (but not reappraisal), as indicated by higher self-reported arousal after distraction in stressed compared to non-stressed participants.

In contrast to these studies indicating detrimental stress effects on cognitive emotion regulation, there is some evidence that emotion regulation might actually benefit from stress exposure as indicated by increased reappraisal success when tested directly after laboratory stress induction (in male participants only; Langer et al., 2020) or at about 90 min after the administration of external cortisol (Jentsch et al., 2019). Hence, the previous studies on stress and emotion regulation show significant inconsistencies in results, which are further underlined by a recent neuroimaging study (Shermohammed et al., 2017). Here, the authors report no stress effect at all, neither on emotional reactivity, nor on reappraisal success and

neither in subjective ratings, nor in brain activity. A possible interpretation of these conflicting results may be related to the experimental set-up of this study. Shermohammed and colleagues (2017) confronted their participants with interleaved blocks of stress induction (i.e. challenging mental arithmetic) and emotion regulation while lying in the magnetic resonance imaging (MRI) scanner. Considering the fine-tuned dynamics of the stress response, this interleaved block design with multiple stress onsets might have resulted in repetitive baseline shifts of the endocrine stress systems. Hence, it may well be that emotion regulation was assessed at a point in time when (nor)adrenalin and cortisol did not yet exert their full effects on the brain and the body. To avoid this problem, the present study employed a stress protocol with one distinct stress onset, short stress duration, and a strict separation from the emotion regulation task. Taken together, the heterogeneous findings of previous studies do not provide clear evidence as to what extend and under what circumstances stress affects subsequent emotion regulation and if this stress effect differs between emotion regulation strategies.

The aim of the present study was to systematically investigate acute stress effects on emotion regulation using fMRI methodology and a between-subject design comparing a stress and a control group. We used the Scan*STRESS*-C for stress induction, which has proven effective in eliciting significant multidimensional stress responses in an fMRI setting (Sandner et al., 2020). The Scan*STRESS*-C consists of one control and one stress phase of only six minutes each and thereby provides a short protocol with one distinct stress onset (and offset) to investigate stress effects on subsequent processes, here cognitive emotion regulation (for details, see Methods section, chapter 3.3.3). The emotion regulation paradigm started 20 minutes (and lasted until 40 minutes) after stress onset, when cortisol concentration is usually at its peak (Kirschbaum & Hellhammer, 1989; Kudielka et al., 2009). To assess emotion regulation abilities, we used the Cognitive Emotion Regulation Task (CERT; Kanske et al., 2011), in which participants were instructed to view neutral and negative pictures and respond naturally to them (*view*), or to *reappraise* the content of these pictures to decrease upcoming negative emotions, or to *distract* themselves by solving a math equation presented on the picture as overlay (see chapter 3.3.5 for details). We hypothesized that a significant stress response elicited by the Scan*STRESS*-C would affect subsequent cognitive emotion regulation, manifested as group differences in both outcome variables of the CERT, i.e. subjective emotional state ratings as well as brain activity during emotion regulation. In detail, we expect more negative emotional ratings and less amygdala

reduction during emotion regulation in the stress compared to the control group. When comparing both regulation strategies, we expect distraction to be more impaired by stress than reappraisal in accordance with Kinner and colleagues (2014).

3.3 Methods

3.3.1 Participants

Eighty-one participants (40 women; 78 right-handed) at the age of 18 to 42 years (M = 24.47, SD = 4.49) were recruited for participation via flyer and postings at the university and university medical center Mainz, Germany. Subjects were randomly assigned to either a stress group (SG; n = 40) or control group (CG; n = 41), which did not differ in age or Body Mass Index (BMI), see Table 2-1. All participants underwent a telephone screening to preclude acute or chronic diseases, a history of and current mental disorders, past or ongoing psychotherapy treatment, a history of neurological, cardiovascular, or endocrine diseases, use of steroid-based lotions or asthma sprays, and smoking behavior or use of opioids or cannabis. Participants with a BMI (kg/m²) below 18 and over 26 were excluded. To reduce variability in cortisol responses related to hormonal alterations throughout the menstrual cycle phase, the intake of oral contraceptives was an additional and mandatory inclusion criterion for female participants. The study was approved by the local ethics committee of the Psychological Institute of the Johannes Gutenberg University Mainz according to the declaration of Helsinki. Participants were compensated for their time with 60 Euros or received course credits.

3.3.2 Procedure

The experimental procedure lasted approx. 2.5 hours (see Figure 2-1A). We provided a cover story informing participant of the alleged study aim (i.e. the investigation of neural activity patterns in performance situations) to ensure the authenticity of the experimental stress paradigm. Participants subsequently completed questionnaires on the state of their well-being (*Mehrdimensionaler Befindlichkeitsfragebogen*, MDBF1, see chapter 3.3.4) as well as a training session of the MRI-tasks (Scan*STRESS*-C and CERT, see chapters 3.3.3 and 3.3.5). They then provided a first saliva sample (S1) using a Salivette® device (Sarstedt AG & Co, Nümbrecht, Germany). Hereafter, they watched a relaxing movie for approx. 30 min. When entering the MR scanner, participants again indicated their emotional state

(MDBF2) and provided another saliva sample (S2). The MRI session started with a localizer (for details on fMRI acquisition and analysis, see chapter 3.3.6), followed by the Scan*STRESS*-C (see chapter 3.3.3) and a third saliva sample (S3) as well as MDBF3. In-MR samples were taken by moving the bench outside the scanner only far enough for the experimenter to place a Salivette in the participants' mouth for two minutes, but the bench was never removed from the scanner completely (see Dedovic et al., 2005 for details on the in-MR sampling procedure). After approx. 6 min of anatomical measures, participants provided another saliva sample (S4) and started the CERT (see chapter 3.3.5), which then took place 20-40 min after stress onset. After participants left the scanner, they again provided a saliva sample (S5) and indicated their current emotional state (MDBF4). Finally, they were debriefed in detail and provided a final saliva sample (S6).

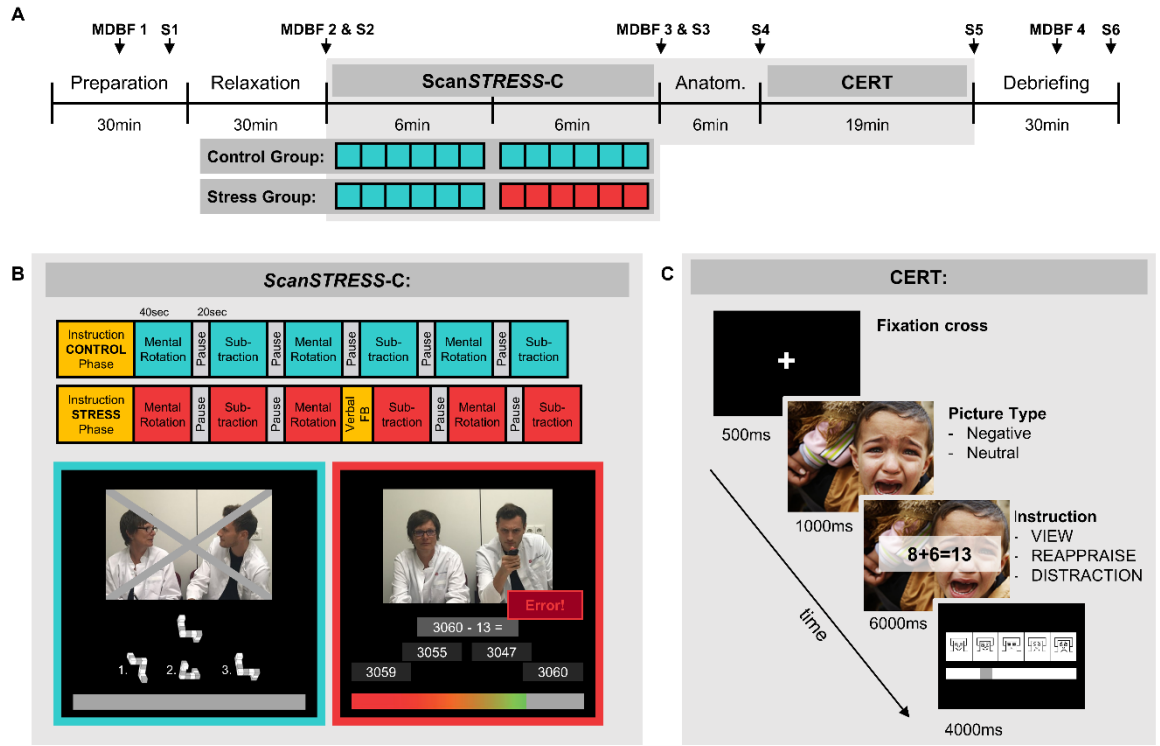

Figure 2-1. Overview of experimental procedure. (A) Schematic of the complete experimental session, including the MRI part (light gray) and the experimental tasks (dark grey), as well as saliva sampling and MDBF rating. (B) Details on the Scan*STRESS*-C procedure (Sandner et al., 2020), consisting of a control phase and a stress phase of six blocks each, including easy or difficult tasks of mental rotation and subtraction (see chapter 3.3.3). (C) Sequence of events in a trial of the CERT paradigm (Kanske et al., 2011, see chapter 3.3.5). FB = feedback; MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol samples.

3.3.3 Stress Paradigm: Scan*STRESS*-C

For in-MR stress induction, we used the Scan*STRESS*-C (Sandner et al., 2020), which is the compact version of the Scan*STRESS*, an established stress paradigm in fMRI research (Streit et al., 2014). The paradigm consists of two phases: an initial control phase and a subsequent stress phase of approx. six minutes each. Each phase consists of six blocks of task performance lasting 40 sec per block, interleaved with 20 sec pauses (see Figure 2-1B). During the stress blocks, participants had to perform two types of cognitive challenging tasks, mental rotation and arithmetic subtraction, within a given time frame as indicated by a countdown bar. Task speed and difficulty were preprogrammed to adjust to the participants' performance to increase the likelihood of failure. While performing these tasks, participants were shown a live video of a jury (two lab members in white coats), sitting in front of the scanner, and observing the participant's performance to further induce social-evaluative elements. In case of slow or incorrect answers, the jury used a red buzzer to give negative feedback in terms of short written instructions (e.g. "Error!"). In between the stress phase, the jury additionally gave standardized verbal feedback via speakers, indicating that the participant's performance so far was below average, and that maximum effort is needed for the sake of good data quality. During control blocks, participants performed simple figure- and number-matching tasks in the absence of visual and verbal jury feedback and time-pressure. In this case, the jury in the video stream remained passive, did not look into the camera, and the video picture was overlaid by a grey diagonal cross to signal the absence of active monitoring (see Figure 2-1B). While the SG passed through an initial control and a subsequent stress phase as described above, participants of the CG underwent two control phases instead (see Figure 2-1A).

3.3.4 Acute Stress Reactivity Measures

Stress responses to the Scan*STRESS*-C, were assessed by (1) subjective well-being ratings at four time points using the *Mehrdimensionaler Befindlichkeitsfragebogen* (Steyer et al., 1997). The MDBF consists of 24 adjectives reflecting positive or negative emotional states. The participants' ratings on a five-point Likert scale can be summed up to a total score of subjective well-being where higher scores reflect a more positive emotional state. Sufficient reliability (Cronbach's alpha $\alpha = .80$ to .92) and validity of the MDBF was confirmed in several studies (Buckert et al., 2014; Klinkenberg et al., 2016; Plessow et al., 2011). In the present study, Cronbach's alpha of $\alpha = .91$ indicated excellent internal consistency. (2) We collected six saliva samples to ensure frequent monitoring of the cortisol

stress response. All saliva samples were stored at -20°C and sent to the Institute of Biopsychology at the Technical University Dresden, Germany, for analysis. Salivary concentrations were measured using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra- and interassay coefficients were below 8%. (3) We recorded heart rate (HR) data with an MR-compatible pulse-oximeter with an infrared emitter placed on the left index finger (50 Hz sampling). And (4), we analyzed BOLD responses during the Scan*STRESS*-C phases as well as during the emotion regulation task (see chapter 3.3.6).

3.3.5 Emotion Regulation Paradigm: CERT

To assess emotion regulation in the aftermath of acute stress exposure, we used the Cognitive Emotion Regulation Task (CERT), previously described and validated in several studies (Heissler, Kanske, Schönfelder, & Wessa, 2014; Kanske et al., 2011, 2012, 2015). During the CERT (see Figure 2-1C), participants are presented with images of either neutral or negative content. All pictures were taken from the EmoPicS stimulus database (Wessa et al., 2010). They were landscape in orientation and matched for content and complexity. After one second of stimulus presentation, participants are given one of three different instructions (1 sec, transparent overlay): (1) they are instructed to just *view* the image and respond naturally to it; (2) they are asked to indicate as fast as possible, if the given math equation is correct or incorrect via button press (*distraction*); (3) participants are asked to *reappraise* the content of the image with the aim to decrease their upcoming negative emotional reaction to it. For the *situational reappraisal* condition, participants were instructed not to distract themselves by thinking of e.g. the next trip to the supermarket, but to stay in the displayed scene of the given image and find another interpretation for it, e.g. a positive ending of the situation. Each trial ended with a rating (4 sec) of the participants' current emotional state on a 9-point scale using the Self-Assessment Manikins (SAM, Bradley & Lang, 1994) ranging from unpleasant to pleasant with higher values indicating more positive emotions. The inter-trial interval (ITI) was jittered from 3 sec to 5 sec. In our study, the CERT consisted of 75 trials of approx. 14.5 sec each: 15 trials each for the following conditions: view_negative, view_neutral, distract_negative, distract_neutral, and reappraise_negative. In total, the CERT lasted approx. 19 min.

3.3.6 fMRI Acquisition and Analysis

We acquired imaging data on a 3T scanner (Siemens Trio, Erlangen, Germany) with a 32-channel head coil. The following parameters were used for anatomical images: slice thickness = 1 mm; FoV = 250 mm; voxel size = 1 mm isotropic; TR = 1900ms; TE = 2.52 ms; flip angle = 9°. Functional images during the Scan*STRESS*-C and CERT were acquired using identical echo planar imaging (EPI) multiband sequences with the following scanning-parameters: slice thickness = 2.5 mm; FoV = 210 mm; voxel size: 2.5 mm isotropic; TR = 1000 ms; TE = 29 ms; flip angle = 56°; multiband acceleration factor = 4. Preprocessing and statistical analysis were conducted using Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm). To account for inhomogeneities of the magnetic field, we discarded the first four images of each sequence. Images were realigned to the first functional image by a 6-parameter rigid body transformation, then co-registered to the anatomical T1 scan, transformed to the Montreal Neurological Institute (MNI) EPI reference space (voxel size: 2 mm isotropic) and smoothed with a 6 mm full-width at half-maximum Gaussian filter.

Analysis of ScanSTRESS-C fMRI Data

As a manipulation check for successful stress induction, individual subjects' data of the Scan*STRESS*-C were analyzed within a general linear model framework including one regressor for the 6 min control phase modelling the onsets and duration of the 40 sec control blocks, and (in case of SG participants) two stress regressors modelling the 40 sec stress blocks, as the stress phase was split into two sequences due to the verbal feedback. The 20 sec pauses in between the active control or stress blocks served as an implicit baseline. In addition, we included six motion regressors as covariates of no interest to control for residual motion artefacts after reorientation. First level analysis was performed for the SG and CG separately. We computed contrast images of [stress vs. control] for each participant of the SG or [control1 vs. control2] for the CG to investigate the general effect of task (stress induction). For second level analysis, we used a two-sample *t*-test to examine group differences in the general effect of acute stress, i.e. [stress vs. control] for the SG and [control1 vs. control2] for the CG. Imaging results of the main task effects were corrected via family-wise error (FWE) for multiple comparisons at a significance level of $p_{\text{whole\_brain}} < .05$.

Analysis of CERT fMRI Data

The statistical model for the CERT data included individual statistical parametric maps to elucidate: (A) the emotional reactivity per se (view_negative vs. view_neutral), (B) the distraction effect (distract_negative vs. view_negative), and (C) the reappraisal effect (reappraise_negative vs. view_negative). We calculated two types of second-level random-effects analyses including the six movement parameters calculated during realignment as parameters of no interest to control for movement artifacts: First, we conducted one-sample *t*-tests on the above-mentioned individual contrast images (A) to (C) of the entire sample to test the general effect of both emotion regulation strategies. Second, we used two-sample *t*-tests to check for group differences in distraction and reappraisal activation patterns. For visualization purposes, we additionally calculated one-sample *t*-tests in both groups separately, see Figure 2-4. To correct for multiple comparisons, imaging results were corrected via family-wise error (FWE) at a significance level of $p_{\text{whole\_brain}} < .05$. Note, that we additionally performed a region of interest (ROI) analyses using MNI coordinates from the meta-analysis by Buhle et al. (2014) to compare ROI activity between groups, but results did not differ from the whole brain analysis (see Supplement 2-1).

3.3.7 Statistical Analyses of Affective, Endocrine, and Physiological Data

Statistical analysis of affective, endocrine, and heart rate data as well as analysis of subjective CERT data was carried out using SPSS 22 (SPSS Inc., Chicago, IL, USA). For all analyses of variance (ANOVAs), which will be described below, statistical effects were evaluated using the Greenhouse–Geisser correction when appropriate.

As a manipulation check, we analyzed group differences in acute stress reactivity to the Scan*STRESS*-C: (1) Regarding changes in subjective well-being, we analyzed MDBF data using a two-way mixed ANOVA with “time” (4 levels, within-subject factor) and “group” (2 levels, between-subject factor). (2) Cortisol data was logarithmized to base 10 to reduce typical data skewness. Changes in saliva cortisol within both groups were compared using a two-way mixed ANOVA with “time” (6 levels) as within-subject factor and “group” (2 levels) as between-subject factor. (3) For HR data, we conducted a two-way mixed ANOVA with “time” (2 levels, within-subject factor) and “group” (2 levels, between-subject factor). As some studies report sex differences in acute stress reactivity (Kudielka & Kirschbaum, 2005), we included “sex” as a covariate in all ANOVAs.

To test for group differences in emotion regulation, we conducted a two-way ANOVA on the CERT ratings with “task” (5 levels for the 5 task conditions, i.e. view_negative, view_neutral, distract_negative, distract_neutral, and reappraise_negative, see chapter 3.3.5) as a within-subject factor and “group” (2 levels) as between-subject factor.

Table 2-1
Group comparisons with means (standard deviations) and statistical parameters for all relevant variables.

	SG		CG			
	N	*M (SD)*	*N*	*M (SD)*	*t* (*df*)	*p*
Sample characteristics						
Age	40	23.85 (4.07)	41	25.07 (4.89)	1.22 (79)	.225
BMI	40	22.30 (1.79)	40	22.08 (2.02)	0.53 (78)	.599
Stress reactivity						
S1 (-37min)	38	3.61 (3.21)	36	3.20 (1.93)	0.68 (72)	.500
S2 (-10min)	38	2.85 (1.59)	36	2.89 (1.51)	-0.28 (72)	.782
S3 (+6min)	38	3.67 (2.28)	36	2.86 (1.29)	1.78 (72)	.078
S4 (+16min)	38	5.12 (4.61)	36	2.74 (1.02)	3.09 (72)	.004**
S5 (+52min)	38	4.68 (4.28)	36	2.70 (1.28)	2.69 (72)	.009**
S6 (+62min)	38	4.38 (5.15)	36	2.58 (1.49)	2.03 (72)	.044*
MDBF 1 (-40min)	38	12.04 (1.58)	37	12.36 (1.50)	0.74 (73)	.464
MDBF 2 (-10min)	38	11.72 (1.72)	37	11.86 (1.47)	0.28 (73)	.781
MDBF 3 (+6min)	38	10.56 (2.09)	37	12.04 (1.58)	3.30 (73)	.001**
MDBF 4 (+50min)	38	11.70 (1.90)	37	12.14 (1.47)	1.45 (73)	.150
HR phase 1	30	73.38 (15.08)	36	72.09 (14.69)	0.35 (64)	.727
HR phase 2	30	81.66 (16.93)	36	70.14 (13.89)	3.04 (64)	.003**
CERT SAM ratings						
View_neutral	38	6.06 (0.78)	38	6.01 (0.76)	-0.29 (74)	.777
Distract_neutral	38	5.75 (0.86)	38	5.80 (0.78)	0.28 (74)	.782
View_negative	38	3.63 (0.92)	38	3.73 (1.02)	0.47 (74)	.640
Distract_negative	38	3.79 (0.96)	38	4.08 (1.24)	1.14 (74)	.260
Reappraise_negative	38	4.70 (0.90)	38	4.74 (1.12)	0.16 (74)	.877

Note. CERT = Cognitive emotion Regulation Questionnaire; CG = Control Group; BMI = Body Mass Index; HR = Heart Rate; MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol samples; SAM = Self-Assessment Manikins; SG = Stress Group. *$p < .05$, **$p < .01$.

3.4 Results

3.4.1 Manipulation Check: Stress Responses to the Scan*STRESS*-C

To verify successful stress induction by the Scan*STRESS*-C, we analyzed group differences in temporal fluctuations of (1) subjective well-being, (2) saliva cortisol concentrations, (3) heart rate, and (4) BOLD-responses. Table 2-1 displays means and standard deviations for each group for all except BOLD-response data.

(1) MDBF data from five participants were missing due to technical problems. The two-way ANOVA on MDBF mean scores resulted in a significant time by group interaction effect after controlling for sex, $F(3,\ 216) = 8.26$, $p > .001$, partial $\eta^2 = .10$ (Greenhouse-Geisser corrected, $\varepsilon = .80$). Post-hoc *t*-tests revealed a significant difference between the SG and the CG at MDBF3, $t(75) = 3.30$, $p = .001$, indicating more negative mood ratings in the SG after the Scan*STRESS*-C, see Figure 2-2A.

(2) For endocrine analyses, we excluded four participants due to missing cortisol values and another three participants with cortisol values < 3 *SD* of the group mean. The two-way ANOVA revealed a significant interaction effect "time*group" after controlling for sex, $F(5,\ 280) = 3.18$, $p = .034$, partial $\eta^2 = .04$ (Greenhouse-Geisser corrected, $\varepsilon = .59$). Post-hoc *t*-tests revealed a significant difference between the SG and the CG at sampling point S4, S5, and S6, see Table 2-1 and Figure 2-2B.

(3) For HR analyses, we had to exclude 14 participants due to recording issues, resulting in subsamples of $n_{stress} = 30$ and $n_{control} = 36$. The two-way ANOVA revealed a significant "time*group" interaction after controlling for sex, $F(1,\ 63) = 31.99$, $p > .001$, partial $\eta^2 = .34$, indicating a significant difference in mean HR between the SG and the CG after stress (see Table 2-1 and Figure 2-2C).

(4) For MRI analyses, one participant had to be excluded due to anatomical abnormalities. We analyzed significant group differences in activations and deactivations, contrasting both experimental phases of the Scan*STRESS*-C, i.e. [stress vs. control] for the SG and [control1 vs. control2] for the CG. Compared to the CG, participants of the SG showed significant activity increases in structures of the salience network, i.e. the bilateral anterior insula, the SMA, the dACC, and the brainstem (all *p*s < .001, whole-brain FWE-corrected). Further activations were found in the parietal, and frontal inferior cortex and the cerebellum. Furthermore, we found strong deactivations in the SG compared to the CG in medial regions of the prefrontal cortex, the posterior cingulate cortex, temporal regions, as

well as the posterior insula cortices (see Supplement Table ST2-2 for further details on significant local maxima with MNI coordinates and *Z* values).

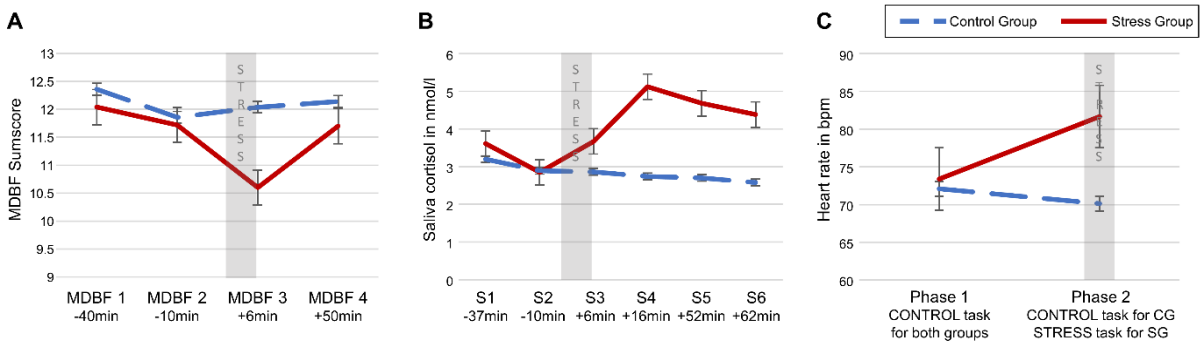

Figure 2-2. Acute stress reactivity on multiple response levels. (A) Mood ratings and (B) saliva cortisol level at respective time points, as well as (C) heart rate values during the two phases of the Scan*STRESS*-C. MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol levels (untransformed). Error bars represent *SEM*.

3.4.2 Stress-Related Changes in Emotion Regulation

To investigate stress effects on emotion regulation, we checked for group differences in (1) subjective affect ratings as well as (2) BOLD responses to the CERT trials. (1) For the subjective CERT ratings, we had to exclude two participants due to missing data and another two with mean values > 3 *SD* of the group mean. The ANOVA on emotion regulation resulted in a significant main effect of "task", $F(4, 296) = 157.06$, $p > .001$, partial $\eta^2 = .68$. Post-hoc *t*-tests comparing the different trial conditions revealed significant differences between view_negative and both, distract_negative ($t(76) = 2.10$, $p_{corr} = .039$) and reappraise_negative ($t(76) = 8.41$, $p_{corr} < .001$, see Table 2-1 for *M* and *SD*). There was no significant interaction effect of "task*group" in the CERT ratings, revealing no differences between experimental groups in emotion regulation or emotional reactivity, see Figure 2-3.

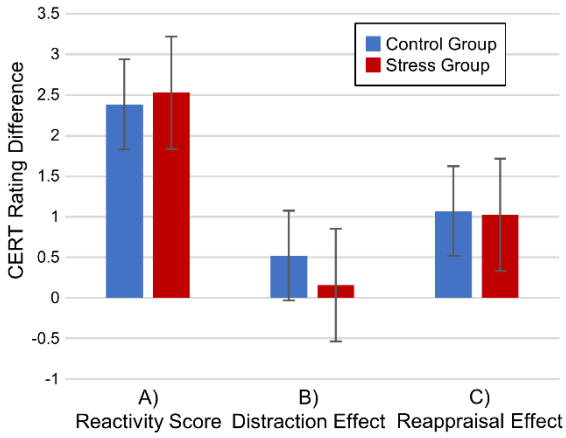

Figure 2-3. Difference scores of CERT ratings: (A) Reactivity score (view_neutral-view_negative), (B) Distraction effect (distract_negative-view_negative), and (C) Reappraisal Effect (reappraise_negative-view_negative). Groups do not differ in any CERT Score. Error bars represent *SEM*.

(2) Analyses of the BOLD responses in the entire sample revealed increased activity in the occipital cortex, the thalamus, and the brainstem when contrasting view_negative vs view_neutral. In addition, we found an extensive network of lateral and medial prefrontal, parietal, and lateral temporal regions showing stronger activity during distraction and reappraisal of negative images compared to viewing negative images (see Table 2-2). In addition, the anterior insula showed increased activity for the distraction, but not the reappraisal contrast. Similarly, we found significant deactivated clusters in the amygdala, the ventromedial prefrontal cortex (vmPFC) and subgenual anterior cingulate cortex (sgACC) only for the distraction, but not the reappraisal contrast, where we found significant deactivations in the posterior insula, see Table 2-2.

To identify group differences in brain activation during the CERT task conditions, we used a two-sample *t*-tests, revealing no significant clusters: the groups did not differ in their activation, neither for (A) emotional reactivity, nor (B) for distraction or (C) reappraisal. In fact, the brain activation pattern was very similar across the two groups, see Figure 2-4.

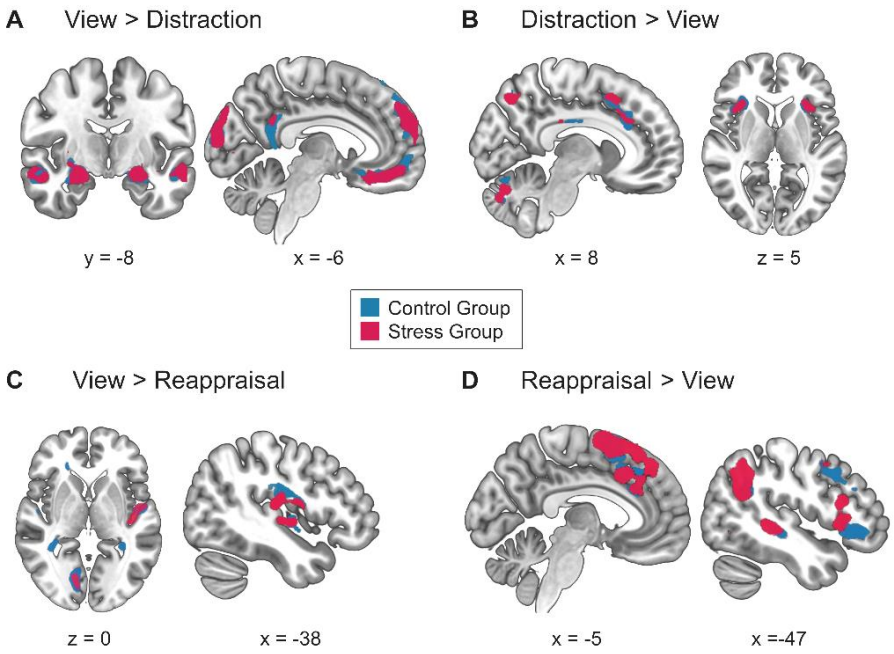

Figure 2-4. Whole brain fMRI analyses examining activations and deactivations of the distraction contrast (A, B) and the reappraisal contrast (C, D). Images are p <.05, whole-brain FWE-corrected, and have been further thresholded at z = 7 (distraction contrast) and z = 4 (reappraisal contrast) for visualization purposes. For graphical display, MRIcroN (https://www.nitrc.org/projects/mricron) was used with the MNI template brain. FWE = family-wise error corrected for multiple comparisons; MNI = Montreal Neurological Institute.

Table 2-2
MNI coordinates of peak voxels and corresponding T and $p_{\_FWE}$ values of activation clusters that show significant activation when contrasting the experimental conditions of the CERT in the whole sample.

Brain structure		**MNI coordinates**			**Statistical values**		
		x	y	z	*k*	Mean *T*	$p_{\_FWE}$
Emotional Reactivity contrast							
[view_negative vs. view_neutral]							
Middle occipital gyrus	R	46	-74	6	16468	15.49	< .001
	L	-34	-86	0			
Cerebellum	L	-6	-76	-34	209	8.46	< .001
Thalamus	R	22	-28	0	46	7.65	< .001

Cerebellum	R	8	-74	-34	35	7.33	< .001
Inferior parietal gyrus	R	32	-50	56	131	7.27	< .001
Brainstem	L	-6	-28	-6	18	6.75	.001
Thalamus	L	-20	-30	2	36	6.02	< .001
[view_neutral vs. view_negative]							
No suprathreshhold clusters							
Distraction contrast							
[distract_negative vs. view_negative]							
Inferior parietal gyrus	L	-42	-42	50	24768	19.91	< .001
	R	42	-40	46			
Middle frontal gyrus	L	-24	2	56			
Anterior insula cortex	L	-30	18	6			
Supplementary motor area	M	2	12	48			
Cerebellum	R	28	-60	-26	4115	18.37	< .001
Inferior temporal gyrus	L	-52	-56	-10	682	15.28	< .001
Anterior insula cortex	R	32	22	4	961	14.94	< .001
Inferior frontal gyrus	R	44	38	26	1738	12.57	< .001
Cerebellum	L	-30	-56	-34	1211	12.40	< .001
Middle frontal gyrus orbital	R	26	50	-12	319	9.43	< .001
Inferior temporal gyrus	R	58	-50	-12	188	8.51	< .001
Middle frontal gyrus orbital	L	-22	42	-14	36	7.79	< .001
Inferior occipital gyrus	L	-24	-96	-10	122	7.44	< .001
Inferior frontal gyrus orbital	R	52	8	22	193	7.38	< .001
[view_negative vs. distract_negative]							
Amygdala	R	22	-8	-14	24946	18.45	< .001
	L	-20	-12	-18			
Superior occipital gyrus	L	-12	-98	24			
Rectus gyrus	L	-2	40	-20	5974	14.42	< .001
	R	4	48	-14			
Middle frontal gyrus	L	-4	52	-12			

Angular gyrus	L	-52	-70	28	1073	11.13	< .001
Inferior frontal gyrus orbital	R	38	34	-14	655	10.89	< .001
	L	-52	26	4	109	9.43	< .001
Cerebellum	R	30	-80	-34	229	9.18	< .001
	L	-20	-82	-36	188	6.44	< .001
Reappraisal contrast							
[reappraise_negative vs. view_negative]							
Supplementary motor area	L	-6	8	66	18825	14.07	< .001
Middle temporal gyrus	L	-52	-34	-2			
Middle cingulate cortex	L	-4	16	42			
Middle frontal gyrus	L	-40	4	51			
Cerebellum	R	38	-60	-28	3361	10.97	< .001
Superior temporal gyrus	R	50	18	-22	3396	10.22	< .001
Orbito frontal gyrus	R	50	34	-8			
Fusiform gyrus	L	-30	-60	-10	4564	9.48	< .001
Middle occipital gyrus	L	-36	-88	8			
Middle temporal gyrus	R	48	-34	-2	712	9.33	< .001
Caudate	L	-14	4	16	724	8.42	< .001
Inferior parietal gyrus	R	54	-54	32	483	8.13	< .001
Caudate	R	16	12	10	502	8.01	< .001
Posterior cingulate cortex	L	-10	-46	34	477	7.31	< .001
Precuneus	L	-8	-54	35			
Superior occipital gyrus	R	24	-74	42	76	6.65	< .001
Superior parietal gyrus	R	26	-60	62	28	6.15	< .001
[view_negative vs. reappraise_negative]							
Superior temporal gyrus	L	-48	-8	0	50	6.92	< .001
Rolandic operculum	L	-40	2	14	39	6.75	< .001
Posterior insula cortex	L	-38	-18	12			
Lingual gyrus	R	14	-76	-2	64	6.16	< .001

Note. L = left hemisphere; R = right hemisphere; M = medial; *k* = cluster size in voxels; MNI = Montreal Neurological Institute.

3.5 Discussion

The aim of the present study was to investigate the potentially detrimental effects of acute stress exposure on the cognitive regulation of negative emotions. Although we were successful in inducing stress by means of the in-MR procedure Scan*STRESS*-C, we did not confirm our hypothesis of impaired cognitive emotion regulation in the face of acute stress neither with respect to *distraction* nor with respect to situation-focused *reappraisal*. Notwithstanding, we found a significant emotion regulation effect for both distraction and reappraisal in the entire sample.

Manipulation Check: General Stress Effects

As the present study was set out to investigate stress-related impairments of cognitive emotion regulation, we first checked for significant changes in dependent variables measuring stress effects, i.e. subjective affect, saliva cortisol, heart rate and BOLD-responses. As in our validation study (Sandner et al., 2020), the Scan*STRESS*-C successfully induced stress in the SG as compared to the CG, as indicated by more negative affective state, higher saliva cortisol secretion, and increased heart rate after stress in the SG (see Figure 2-2). Further, individuals of the SG showed increased BOLD responses in structures of the salience network in stress as compared to control blocks. These acute stress effects found in the SG are in line with previous fMRI studies on acute stress effect (Dahm et al., 2017; Quaedflieg et al., 2013; Streit et al., 2014).

General Emotion Regulation Effects

General analyses of the CERT data, independent of the experimental group, revealed a significant emotion regulation effect in the whole sample: *distraction* as well as *reappraisal* of negative pictures resulted in reduced negative emotional state ratings and increased cognitive control network activity compared to passive viewing of negative pictures. Interestingly, only the distraction contrast, not the reappraisal contrast, resulted in reduced BOLD responses in the amygdala, the vmPFC, and sgACC. This is surprising, as in the subjective ratings, reappraisal resulted in a stronger reduction of negative emotions compared to distraction (see Figure 2-3). However, this pattern is in line with various other studies reporting stronger amygdala downregulation for distraction but more pronounced decreases in self-reported negative affect for reappraisal (Jentsch et al., 2019; Kanske et al., 2011; McRae et al., 2010). Since the amygdala is known to be in involved in the detection and processing of negative affective stimuli (Phelps & LeDoux, 2005), it is suggested that

reappraisal, in contrast to distraction, leads to a more elaborate processing of the negative content of the picture. Hence, amygdala activity may be maintained during reappraisal, whereas distraction involves a shift of attention away from the emotion triggering information, resulting in stronger reduction of BOLD responses in the amygdala (Jentsch et al., 2019).

Stress Effects on Emotion Regulation

Our main hypothesis, i.e. a stress-related impairment of cognitive emotion regulation capacities, was not confirmed by the present study. Although we found a significant stress response in the SG on multiple response levels, these stress effects did not affect subjective ratings and brain activation during emotion regulation. There were no group differences, neither in emotional reactivity (i.e. view_neutral - view_negative), nor in cognitive emotion regulation via distraction (i.e. distract_negative - view_negative), or reappraisal (i.e. reappraise_negative - view_negative). The lack of group differences was present for all dependent variables, i.e., subjective affect ratings and BOLD responses in the cognitive control and emotion processing networks. This is surprising, since Kinner and colleagues (2014) reported a significant stress-related impairment at least in distraction. Furthermore, acute stress has been shown to impair anger regulation (Zhan et al., 2017) as well as to undermine an emotion regulation training of previously fear conditioned stimuli (Raio et al., 2013). These studies have used subjective ratings and skin conductance responses to indicate emotion regulation success. Our results are in line with Shermohammed and colleagues (2017), the only neuroimaging study which investigated the effects of psychosocial stress exposure on emotion regulation effectiveness so far. This study also failed to find a stress effect on emotional reactivity or cognitive emotion regulation effectiveness in an experimental set-up where the emotion regulation task was interleaved with stressful mental calculation. In contrast to their study design, our stress task provided one distinct stress onset and offset with a cognitive emotion regulation task following 20-40 min after stressor onset, i.e. when cortisol secretion is suggested to peak. Yet, despite these differences in study design, our study also failed to show stress-related impairments in emotion regulation effectiveness on a subjective as well as neural level. Our study therefore further suggests that a clear and direct effect of acute stress on emotion regulation is not detectable at least at this time window and in this specific laboratory fMRI set-up. In a further study of our group, we investigated the effects of a psychosocial stressor on situational reappraisal by means of electroencephalography (EEG), electromyography (EMG), and self-report affect

(unpublished data). In line with the present study, we did not find an effect of stress at a similar time window (20-40 min after stress onset). However, reappraisal was impaired by stress in a later CERT phase (40-60 min after stress onset) as indicated by significant group differences in the reappraisal effect. These results suggest that *timing* might play an important role in the context of stress and emotion regulation. In another recent study, Jentsch and colleagues (2019) administered 30 mg external cortisol 90 min prior to the CERT and reported an enhancement in emotion regulation, i.e. significantly more negative ratings to the view condition compared to the distraction and reappraise condition. Although cortisol administration certainly differs from real-life or laboratory stress induction, this study provides first evidence for a delayed cortisol-induced facilitation of cognitive emotion regulation processes in the aftermath of stressful events, which is further confirming the decisive role of *time* in the dynamic interplay of stress and emotion regulation.

Taken together, these results indicate that emotion regulation abilities in the face of stress might follow a particular time pattern, with rather preserved abilities during and shortly after stress (< 40 min; this study and Shermohammed et al., 2017, see also Langer et al., 2020 for a stress-related improvement in cognitive reappraisal in men), then impairment after approx. 40 to 60 min after stress onset (unpublished data of our group), and even improvements 90 min after stress onset (Jentsch et al., 2019). Although this time pattern and its underlying mechanisms certainly need further systematic investigation in future studies, it may be of high practical relevance in the context of interventions aimed at improving stress resilience and coping. Nevertheless, the scarce literature suggests a careful interpretation of these recent results since other influencing factors might be considered. For example, *mental fatigue* might partially explain the emotion regulation impairments in the aftermath of a stressor: Challenging and exhausting stress tasks might lead to greater mental fatigue, which is known to impair emotion regulation in general (Grillon, Quispe-Escudero, Mathur, & Ernst, 2015) and might have a particular impact on emotion regulation performance especially at a later phase of a long experiment. This explanation does not intervene with the results of Jentsch and colleagues (2019) as they induced high cortisol levels through oral administration of cortisol and not through a tiresome psychosocial stress exposure. Given that both studies reporting no stress effect on emotion regulation were fMRI studies (this study and Shermohammed et al., 2017), the tough narrowed and noisy *MRI environment* may be considered an additional constant challenge, possibly interfering with both, the stress induction effects as well as its interaction with emotion regulation processes.

Limitations

Beside the rather homogenous study sample of mainly young and healthy students limiting the generalizability of our results, two methodological limitations of the present study should be considered: First, we assessed emotional responses to the CERT pictures only as subjective ratings of valence on a scale from *unhappy* to *happy*. Future studies might include measures of arousal as well as psychophysiological markers, considering that the impairment in distraction after stress reported by Kinner and colleagues (2014) was only found in arousal ratings, not valence. Second, since the aversive pictures used in the CERT mainly depict scenes of war or crying or injured persons, ecological validity of these stimuli is rather low. This might explain the lack of a stress-related increase in general emotional *reactivity* in our study (see Figure 2-3), which in turn may -at least partly- account for the missing stress effect on emotion *regulation* as there is no stress-related increase in emotional responses to regulate. Another indicator of the lacking emotional *reactivity* to the negative pictures is the missing BOLD response in limbic regions when contrasting negative and neutral pictures during the viewing condition (see Table 2-2). Other studies using the CERT typically report a strong BOLD response of e.g. the amygdala in this contrast (Kanske et al., 2011; Ochsner et al., 2012), indicating the stronger processing of arousing stimuli when viewing negative as compared to neutral pictures. In our study however, the negative and neutral pictures were chosen carefully to minimize differences in complexity and content, (i.e. both mainly depicting human social content). Further, we deliberately chose negative pictures of only moderate intensity to increase the opportunity of generating alternative interpretations (i.e. reappraisals) of the depicted scenes. Thus, the pictures were quite similar with respect to arousal or threat detection, possibly resulting in comparable limbic responding, and emotional *reactivity* and emotion *regulation* possibilities might have been limited. Hence, future studies investigating emotion regulation might consider using stimulus material of higher (or at least systematically varying) emotional intensity and higher personal relevance to the participants.

Outlook and Further Directions

When discussing the present and previous studies, it is important to note that stress and emotion regulation are close constructs that are based on a bidirectional relationship: Acute stress might affect emotion regulation abilities, but recent research suggests that emotion regulation abilities also affect the response to acute stress. Several studies report a main effect of the *habitual use of reappraisal* on acute cortisol reactivity (Raymond, Marin,

Juster, & Lupien, 2019), recovery (Lewis, Yoon, & Joormann, 2018), or HPA axis habituation (Roos, Janson, Sturmbauer, Bennett, & Rohleder, 2019) to an acute stressor. In addition, stress is known to generally lead to more habit-like behavior (Schwabe & Wolf, 2011, 2013; Wirz, Bogdanov, & Schwabe, 2018). Hence, within our stress group, participants with high habitual use of reappraisal or distraction may have benefit from the stress induction, because it promoted the use of their habitual emotion regulation strategies during the CERT, thereby increasing emotion regulation performance after stress. Reversely, for participants who habitually use other emotion regulation strategies (e.g. rumination, catastrophizing), these strategies might have interfered with our CERT task when promoted by the stress induction. To further verify these assumptions, future studies would benefit from assessing habitual emotion regulation in addition to instructed emotion regulation strategies after stress.

Another individual factor possibly affecting the bidirectional relationship of stress and emotion regulation might be *sex*. Besides numerous studies observing sex-differences in both, stress reactivity (Kirschbaum et al., 1999; Liu et al., 2017) as well as emotion regulation effectivity (McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008) and flexibility (Goubet & Chrysikou, 2019), a very recent study additionally discovered that the effect of stress on emotion regulation differs decisively according to differences in sex hormone concentrations: Langer and colleagues (2020) investigated emotion regulation in the face of stress using a similar study design as the present study, with the CERT following approx. 25-50 min after stress onset. Interestingly, the authors report an improvement in emotion regulation outcomes after stress in only male participants, but no such stress-effect in women, suggesting a complex interplay of sex-specific hormones (i.e. estrogens, gestagens, and androgenes) and stress-related neuroendocrine activity (for more information see e.g. McEwen et al., 2016; Ter Horst et al., 2012). Future studies may thus have to investigate if individual differences such as *habitual reappraisal* or *sex* may play a moderating role in the complex bidirectional interaction of stress and emotion regulation.

3.6 Conclusion

In the present study, we systematically investigated cognitive emotion regulation abilities in the face of stress to complement and extend previous studies in this field. Results of our study indicate that there is no direct effect of an acute psychosocial laboratory stressor on emotion regulation 20-40 minutes after stress onset. The relationship of stress and

emotion regulation seems rather complex and may be influenced by several co-varying contextual and individual factors. Hence, when investigating emotion regulation in the face of stress in future studies, careful methodological considerations of the experimental design, i.e. the timing and characteristics of the paradigms used, seem warranted.

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4 Overall Discussion

4.1 General Summary and Further Integration of Findings

This dissertation aimed at investigating the acute stress response in its multifaceted nature in a first step, providing valuable insights in how long-term HPA axis activity affects these acute stress responses in Study 1. In a second step, we reached out to investigate if and how the acute stress response itself affects subsequent ER capacities in Study 2.

Validating the ScanSTRESS-C as an in-MR Stress Protocol

The aim of Study 1 was two-fold: the study was set out, first to implement and validate an experimental paradigm to induce acute stress responses in an MRI-laboratory setting and second to determine the effect of long-term HPA axis activity on these multidimensional acute stress responses. For stress induction, the Scan*STRESS*-C was implemented as an adaptation of the original Scan*STRESS* (Streit et al., 2014). Adaptations included shortening and reorganizing of the experimental blocks (see chapter 2.3.3 and Figure 1-1) to the following needs: the Scan*STRESS*-C provides one distinct stress onset (instead of multiple reoccurring stress onsets in case of alternating stress and control blocks) which proves beneficial when examining the fine-tuned temporal dynamics of the acute stress response. In addition, shortening the total length of the Scan*STRESS*-C to 12 min allows for investigating the impact of acute stress on subsequent processes in an ethically tolerable and ecological valid manner, especially when considering the challenging environment of an MRI-laboratory setting. Results of Study 1 proved the Scan*STRESS*-C to be effective in eliciting significant stress responses on subjective, endocrine, neural, and physiological level (see chapter 2.4.1), further qualifying the Scan*STRESS*-C as a promising tool to investigate stress effects on subsequent neurocognitive processes (e.g. cognitive flexibility or ER; see Study 2). Note, that significant pitfalls of the Scan*STRESS*-C will be discussed in chapter 4.2. Interestingly, the acute stress responses on endocrine and neural level correlated negatively with HCC, a biomarker for long-term HPA axis activity, indicating that the higher long-term HPA axis activity, the lower the neuroendocrine acute stress response. Although the latter finding certainly requires careful interpretation (see chapter 4.2 for methodological considerations), in chapter 4.3 of this dissertation, an attempt to integrate this correlational finding of Study 1 into existing literature on *stress immunization* is made.

Disentangling the Stress Effect on ER: a Competition of Stress Systems?

In Study 2, the Scan*STRESS*-C was used to systematically investigate the effect of an acute stressor on subsequent cognitive ER using fMRI methodology. In a between-subject design, participants underwent either the Scan*STRESS*-C (Stress Group; SG) or a respective control condition (Control Group; CG). About 20 min later, all participants performed the CERT, a cognitive ER task, using attentional distraction and situational reappraisal as ER strategies. Results indicated a significant stress response to the Scan*STRESS*-C in the SG, but not the CG. However, contrary to the hypothesis, this stress response did not affect subsequent ER strategies, neither distraction nor reappraisal: the participants showed successful ER irrespective of being stressed before or not. This result of Study 2 was surprising, since acute stress is believed to come along with downregulated prefrontal areas for the sake of increased salience network activity in the face of stress (Hermans et al., 2014) and cognitive ER is known to rely heavily on prefrontal functioning (Buhle et al., 2014). However, as discussed in Study 2 (see chapter 3.5), the bidirectional relationship of stress and ER appears to be rather complex and influenced by a wide array of contextual (e.g. stimulus intensity, timing) and intrapersonal factors (e.g. sex, fatigue, habitual reappraisal).

To provide a more in-depth discussion of the surprising result of Study 2, (i.e. no effect of an acute laboratory stressor on subsequent cognitive ER) a quick review of the current state of research in this field is required. Interestingly, previous research on stress and ER is characterized by inconsistencies in study results, ranging from ER-impairments (Kinner et al., 2014; Raio et al., 2013; Zhan et al., 2017), to no stress effect on ER (Shermohammed et al., 2017; Study 2 of this dissertation), to even ER-enhancement after stress (Jentsch et al., 2019; Langer et al., 2020), see chapter 3.5 for a detailed discussion. In the search for possible explanation for these inconsistencies, a closer look at the two biological stress systems will be taken: As described in chapter 1.2.2, both the immediate responses of the catecholaminergic system (as part of the SNS) as well as the slower acting corticosteroid system (i.e. HPA axis) contribute to a complex psychophysiological response to acute stress by interacting with peripheral tissue as well as with cortical and subcortical brain regions. Given that the multistage cascade of the HPA axis system is slower-reacting, requiring at least 20-30 min to peak, it may be discussed, if the upregulation of the salience network and downregulation of prefrontal brain regions in the face of stress may mainly be driven by early SNS activity with catecholamines binding to α1-receptors in the PFC (see chapter 1.2.2). Supporting evidence comes from Raio and colleagues (2013) who reported that the impairment in fear regulation after stress was correlated with α-Amylase, a

biomarker for SNS activity (Nater & Rohleder, 2009). No correlation was found for cortisol concentrations. Another study (Hermans et al., 2011) revealed that functional connectivity of the amygdala with other regions of the salience network was diminished when adrenergic activity was blocked (using the β-adrenergic blocker propanolol, 40 mg). No such effect was reported when corticosteroid synthesis was inhibited (by administering 750 mg of metyrapone). Hence, the systematic reallocation of cognitive resources in the face of acute stress (see chapter 1.2.2 and Figure 1) and the regulatory impairments in higher-order cognitive functioning might be primarily mediated by catecholaminergic activity.

Cortisol, on the other hand, has been reported to buffer the increase of negative affect after stress (Het, Schoofs, Rohleder, & Wolf, 2012; Reuter, 2002), to reduce self-reported fear (Soravia et al., 2006), to enhance regulatory activity in the PFC (Jentsch et al., 2019), and to reduce emotion-related activity in the amygdala (Henckens, van Wingen, Joëls, & Fernández, 2010). Hence, it is assumed that in the aftermath of a stressor, late cortisol effects contribute to a restoration of homeostasis and a normalization of brain network activity (De Kloet, 2004; Hermans et al., 2014), including the downregulation of salience network activity and upregulation of the prefrontal executive network (see chapter 1.2.2 and Figure 1). This in turn may explain the reported enhancement in emotion regulatory capacities in the longer aftermath of a stressor (Jentsch et al., 2019).

Relative predominance of the stress systems

Given these fine-tuned temporal dynamics of the neuroendocrine stress systems, it may be assumed, that the relative predominance of one stress system over the other may distinctively determine the intensity (or presence) and direction of a stress effect on ER: if catecholaminergic activity dominates cortisol effects, ER may be impaired. If the cortisol effects outreach catecholamine activity, ER may be even facilitated. This idea of a relative predominance of one system over the other may help to understand the inconsistencies in previous results. A deeper understanding of what factors influence this balance of the stress systems may structure and advance research on the complex bidirectional relationship of stress and ER. It can be assumed, for example, that *timing* certainly influences this balance of the stress systems with SNS activity dominating over HPA axis activity during and shortly after stress and the other way around after approx. 1 h, when catecholamine concentration fades and the late (genomic) effects of cortisol kick in (see also Figure 1). Behavioral evidence for this assumption of a relative predominance of one stress system over the other is provided by studies reporting a decline in prefrontal-based ER especially

when testing took place during high SNS activity (Kinner et al., 2014; Raio et al., 2013; Zhan et al., 2017) and an enhancement in a study testing ER in the longer aftermath of cortisol administration (Jentsch et al., 2019). However, other studies, including Study 2, testing ER in a time-window after stress where SNS axis activity is believed to dominate over HPA axis activity report no significant stress effect on ER (Shermohammed et al., 2017; Study 2 of this dissertation). In contrast, Langer and colleagues (2020) report even an enhancement in ER in male participants. In addition, recent unpublished data of our own group indicates stress-related impairments in ER only at a later phase (40-60 min after stress onset), when adrenergic concentration is supposed to be already levelled (Rimpel et al., not published). These latter findings suggest that *timing* might not be the only decisive factor influencing the relative predominance of one stress system over another.

On closer examination of these inconclusive results, it becomes obvious that study designs also differ in the *type of stressor*. Those studies reporting ER-impairments after stress included a physical stressor, i.e. the Cold Pressure Task (CPT; Lovallo, 1975; Raio et al., 2013), or a social-evaluative version of the CPT (SECPT; Schwabe, Haddad & Schachinger, 2008; Kinner et al., 2014; Zhan et al., 2017). Physical stressors resemble a threat to the goal of physical integrity or self-preservation (Dickerson & Kemeny, 2004) which usually implies a rapid and intense activation of the SNS to mobilize energy resources and enable unpremeditated actions to survive and overcome danger and challenges (fight-or-flight, see chapter 1.2.2). Thus, these physical stressors might have led to a relative predominance of the catecholaminergic system, involving detriments in prefrontal-based functions, in this case ER. In contrast, the other studies reporting no or an enhancing effect of stress on ER used a psychosocial stressor, such as the Trier Social Stress Test (TSST; Kirschbaum, Pirke & Hellhammer, 1993; Langer et al., 2020; Rimpel et al., not published) or the Scan*STRESS*-C (Sandner et al., 2020; Study 2 of this dissertation) or a comparable stress protocol including a speech preparation phase in combination with arithmetic tasks (Shermohammed et al., 2017). These more complex psychosocial stressors, while still being effective in eliciting a significant response of both stress systems (Dickerson & Kemeny, 2004), might be less prone to the rapid dynamics of the sympathetic fight-or-flight response compared to intense physical pain, as used in the aforementioned CPT studies. Thus, a relative predominance of the corticosteroid system over the catecholaminergic system might explain the missing impairments (Shermohammed et al., 2017; Study 2 of this dissertation) or even improvements (Langer et al., 2020) in ER after stress.

To sum up, future studies are encouraged to specifically address the balance of the two stress systems and the impact of a relative predominance of one over the other in the context of stress and ER. So far, Study 2 proves, that cognitive ER abilities survive at least moderate levels of laboratory stress induction. In chapter 4.3 cognitive ER will further be discussed in the context of resilience mechanisms.

4.2 Limitations

When interpreting and discussing the results of the present dissertation, some limitations regarding the methods and analyses applied in Study 1 and Study 2 need to be considered.

First, despite the convincing evidence that the Scan*STRESS*-C elicits acute stress responses, a methodological limitation may limit the applicability and interpretability of the paradigm and needs to be considered when interpreting the findings of Study 1. In contrast to the original Scan*STRESS* (Streit et al., 2014) where stress and control blocks were alternated and randomized, the Scan*STRESS*-C uses a fixed-block design with one distinct control and one distinct stress phase. This fixed-block design served to model a naturalistic, brief, and distinct stress exposure, while unfortunately bearing the risk for systematic order effects: external environmental or technical factors (i.e. signal drift effects of the MR-Scanner) as well as intraindividual processes (i.e. scanner anxiety in MR-naïve participants, fatigue during a long experiment) may exert differential effects on the initial control phase as compared to the subsequent stress phase, inducing a systematic bias and increasing error variance when contrasting both phases. Hence, while the Scan*STRESS*-C certainly represents a promising new methodological approach to investigate the effects of the neural stress response on subsequent psychological processes (see discussion in chapter 4.1), careful consideration of potential order and sequence effects seem warranted when interpreting fMRI as well as behavioral data.

A second limitation of Study 1 pertains to the correlational nature of the HCC-analyses: the conclusion of HCC significantly predicting a blunted stress response as reported in Study 1, was based on the mere correlational finding of HCC correlating with stress-related saliva cortisol increase and stress-related activity in the dACC. As common to all correlative findings, assumptions about the causality of the relationship are limited. Since HCC and saliva cortisol are both products of the HPA axis that, on a neural level, interacts with i.a. the dACC in a complex neuroendocrine response in the face of stress (see chapter

1.2.2), their relationship can be considered far more complex, underlying multifactorial determinants. In concrete terms, the relationship of long-term HPA axis activity and acute stress may in fact be non-linear, i.e. possibly U-curved (see chapter 4.3 for more information on *stress immunization*). In this case, a quadratic regression analysis might be the method of choice to investigate HCC and acute stress in future studies with larger sample sizes.

Third, using the CERT to test ER capacities in Study 2 requires some methodological considerations. Given the complex interplay of stress and ER, a special emphasis should be placed on how these constructs can be operationalised in experimental research. The CERT is a validated experimental paradigm that proved beneficial when investigating different ER strategies due its elementary design and ease of use in an fMRI setting (Kanske et al., 2011, 2012; Schönfelder et al., 2014). However, the CERT is subject to methodological limitations restraining its applicability and informative value. For example, emotion induction in the CERT is merely picture-based. To test different strategies of downregulating intense negative emotions in Study 2, pictures of sufficient intensity and aversiveness were carefully chosen – yet at the expenses of ecological validity. As discussed in chapter 3.5, the pictures mainly depicted scenes of war, crying persons, or injured bodies – thus situations with rather low personal relevance or salience for our participants. Consequently, emotional reactivity to the aversive pictures was rather low, which in turn may have limited ER possibilities. In addition, the CERT is also subject to a high risk of demand characteristics. During reappraisal trials, participants are explicitly instructed to find an alternative reinterpretation of the depicted situation *that makes them feel better*. Hereafter participants indicated their current affective state. No information is assessed on if and how participants tried to reappraise, resembling a ‘black box’.

Recently, there have been few attempts to open that ‘black box’ in ER research, focusing more on the processes underlying ER strategies. Langer and colleagues (2020) took a first step in this direction by asking their participants not only to indicate their current affective state after each trial, but also to specify how successful they were in applying the respective ER strategy. Interestingly, this ‘subjective ER success rating’ correlated significantly and positively with the magnitude of cortisol secretion after stress, underlining further their result of an ER-enhancement after stress. Another attempt to open the ‘back box’ was made by our research group, introducing the Script-based Reappraisal Task (SRT; Zeier, Sandner & Wessa, 2020). The SRT provides a promising alternative to the picture-based emotion induction by using short text scripts that describe everyday situations associated with negative emotions (i.e. fear and anger). After script presentation, participants

are instructed to create as many different reappraisals as possible. In this ideation phase, participants indicate with a button press a new reappraisal coming to mind. After rating their current emotional state on a SAM scale, participants are given a 90 sec recording phase to enter all reappraisals that occurred during the ideation phase. This way, the SRT provides additional valuable outcome measures, i.e. reappraisal fluency (total number of reappraisals) and reappraisal flexibility (diversity of reappraisals). Hence, the SRT constitutes a promising new advancement in ER research by providing a tool for a more in-depth investigation of the (sub-)processes underlying cognitive ER. Future studies will determine if and how these (sub-)processes may be influenced by acute stress.

4.3 Outlook: Stress and Emotion Regulation in the context of Resilience

To provide a comprehensive outlook on possible future research areas, this dissertation's main findings on stress reactivity and its interaction with ER will be discussed in the context of resilience.

According to the American Psychological Association (APA), resilience is defined as "the process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress" (2013, p. 2). Hence, it can be considered the absence of stress-related dysfunctions (see chapters 1.1 and 1.2) after times of adversity (Bonanno, Westphal, & Mancini, 2011; Kalisch et al., 2019, 2014). In the last decades, resilience has become an increasingly popular topic across various research domains, resembling a paradigm shift away from deficit-based categorical psychiatric research (focussing on pathogenesis) to a more transdiagnostic mental health focus (salutogenesis). Contrary to what has long been assumed, resilience is no longer considered as a unitary trait that some people have and others do not, but rather as a flexible construct, that changes over time and contexts as the outcome of a dynamic adaptation to stress (Kalisch et al., 2014). As described in chapters 1.1 and 1.2, when facing acute threat or challenge, the acute stress response may well be primarily adaptive, but also resource demanding to a great extent. Hence, if too intense, prolonged, repeated, or chronified, stress can become deleterious, contributing to severe mental dysfunction (see chapter 1.1). Mechanisms that regulate and fine-tune these stress responses to optimal levels, preserving their primary adaptive function while assuring maximum efficient deployment of resources, can be considered *resilience mechanisms* (Kalisch et al., 2014). In this light, based on this dissertation's main results, stress immunization and cognitive ER may be discussed as potential resilience mechanisms.

Stress immunization. In Study 1, higher HCC was associated with lower cortisol responses to the acute stressor as well as with lower stress-related activity in the dACC, indicating a downregulation of acute stress responsivity in individuals with high HCC. Before further discussing this finding in light of stress immunization, it should be noted however, that any broader interpretation must be treated with caution given the correlational nature of the result (see also chapters 2.5 and 4.2) as well as the multifactorial influences of HCC, i.e. situational, socio-demographic, and genetic factors (Rietschel et al., 2017; Stalder & Kirschbaum, 2012). Nevertheless, when considering HCC as a biomarker for recent stress exposure (Russell et al., 2012; Stalder et al., 2017), the finding of Study 1 might be interpreted in within the concept of *'stress immunization'*.

According to the *'stress immunization'* hypothesis, exposure to mildly stressful events in the past may facilitate adaptive functioning when confronted with stressors later in life by promoting mechanisms that foster resilience. The *stress immunization* hypothesis originates from a number of animal studies in rodents (Brockhurst, Cheleuitte-Nieves, Buckmaster, Schatzberg, & Lyons, 2015) and primates (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006) exposed to moderate early life stress. Seery and colleagues systematically investigated a similar phenomenon in humans (Seery, Holman, & Silver, 2010; Seery, Leo, Lupien, Kondrak, & Almonte, 2013). Their series of studies in a divers national survey sample (N = 2,398) builds on to what has previously been referred to as '*toughness'* (Dienstbier, 1989), *'stress inoculation'* (Meichenbaum, 1993), or *'steeling'* (Rutter, 2006): namely, the effect of moderate stress exposure in the past leaving individuals better able to cope with subsequent stressors by strengthening the body's regulatory systems and promoting the development of elaborate coping skills (Liu, 2015; Seery & Quinton, 2016). In line with this, Lam, Shields, Trainor, Slavich, and Yonelinas (2018) investigated the relationship of acute stress reactivity and cumulative stress exposure, i.e. the total sum of all stressors experienced over the entire lifespan. Greater cumulative stress exposure was a significant predictor of blunted cortisol responses even when controlling for possible confounds, i.e. age, sex, and BMI. Drawing inferences from these findings about the results of Study 1, moderate stress exposure in the previous months as indicated by high levels of HCC may have fostered resilience to future stressors, resulting in blunted responses to the Scan*STRESS*-C.

However, as we did not assess recent or cumulative life stress in Study 1, conclusions on *stress immunization* processes remain speculative. Future studies are needed to systematically investigate the protective or maladaptive psychological and biological

mechanisms underlying the relationship between recent stress exposure or HCC levels and acute stress reactivity. This may preferably be done in longitudinal studies assessing ongoing stress exposure on an ecological momentary assessment (EMA) basis. Alternatively, cross sectional studies may benefit from using natural conditions mirroring systematic stress exposure, such as academic exam period (Viena, Banks, Barbu, Schulman, & Tartar, 2012) or regular physical exercise (Gröpel, Urner, Pruessner, & Quirin, 2018), where a '*cross-stressor adaptation*' effect, resembling '*stress immunization'*, has already been detected in previous studies (Hamer, Taylor, & Steptoe, 2006; Sothmann, 2006).

Cognitive ER. Results of Study 2 indicate that cognitive ER abilities survive the aftermath of a moderate laboratory psychosocial stressor. In this outlook, the focus will be on the inverse effect, i.e. cognitive ER modulating the acute stress response, like a potential resilience mechanism. As mentioned in chapter 3.5, there is considerable evidence showing that ER, especially cognitive reappraisal, significantly affects stress perception and physiology (Lewis et al., 2018; Raymond et al., 2019; Roos et al., 2019). In fact, according to Lazarus and Folkman (1984), the (re-)appraisal of a situation or stimulus may be *the one* decisive factor in the development of stress: here, stress is considered the outcome of an appraisal process, where a stimulus or situation is evaluated as unpleasant or goal-incompatible and perceived to exceed one's coping possibilities (see also chapter 1.2.1).

Promising evidence for a stress regulating effect comes from studies on *trait reappraisal*, i.e. the tendency of an individual to frequently use reappraisal as a habitual ER strategy. Carlson, Dikecligil, Greenberg, and Mujica-Parodi (2012) for example used a real-life stressor, i.e. a first time tandem skydive, to test the effect of self-reported *trait reappraisal* on stress reactivity. Here, *trait reappraisal* was associated with lower stress reactivity, as indicated by lower increases in cortisol and heart rate, as well as lower state anxiety and higher euphoria ratings after the skydive. In another study, *trait reappraisal* was found to significantly predict HPA axis habituation to a repeated stressor in a two-day experiment (Roos et al., 2019). Raymond et al. (2019) investigated the differential effect of adaptive and maladaptive ER strategies (here reappraisal and suppression, respectively) on acute stress responding. Their results suggested that reappraisal buffers the deleterious effects of suppression on both reactivity to and recovery from an acute psychosocial stressor. Further evidence comes from intervention studies implying that a) cognitive reappraisal is trainable in short training sessions (Denny & Ochsner, 2014) and b) that improved reappraisal abilities contribute to attenuated post-treatment stress reactivity (Gaab et al.,

2003). Furthermore, increases in reappraisal abilities were found to mediate the beneficial effects of cognitive behavioral therapy (CBT) in anxiety disorders (Goldin et al., 2012; Smits, Julian, Rosenfield, & Powers, 2012). More intriguingly, cognitive reappraisal is currently discussed as an inherent aspect of the Positive Appraisal Style Theory of Resilience (PASTOR; Kalisch et al., 2014): here, reappraisal is assigned the power to attenuate ongoing stress responses by adjusting negative appraisals or generating complementary positive appraisals. An individual who is better in (volitionally or habitually) generating alternative, more positive appraisals, is considered more likely to produce an overall positive appraisal outcome, which -according to PASTOR- is the key mechanism to resilience (Kalisch et al., 2014).

To sum up, cognitive reappraisal can be considered a powerful psychological tool to regulate stress responses. Study 2 of this dissertation contributes here, by indicating that reappraisal (also distraction) abilities remain intact even when facing an acute stressor. Future studies may pick up here e.g. by disentangling the differential effects of reappraisal and distraction (and other ER strategies) in the context of stress regulation and resilience. This might best be done in longitudinal studies systematically assessing both, ER strategy use (e.g. via specific ER training and/or during CBT) as well as stressor occurrence and intensity (e.g. via laboratory stress induction and/or EMA real-life stress assessment). New insights in these areas would contribute significantly to a deeper understanding of the relationship between stress and ER.

4.4 Conclusion

Given the decisive role of stress in the development and maintenance of various psychiatric and physical disorders (Brown et al., 2004; Kara & Polo, 2014; Kivimäki & Steptoe, 2018; Sinha & Jastreboff, 2013), the phenomenon of stress and its short- and long-term consequences has become an increasingly popular research topic over the last decades across disciplines. This dissertation contributes to this field of research by first providing a detailed characterization of the acute stress response on multiple levels (Study 1) and second, systemically investigating the effect of these acute stress responses on cognitive emotion regulation abilities (Study 2). This dissertation's main findings (i.e. Study 1: a blunted neuroendocrine stress response in individuals with high HCC, and Study 2: emotion regulation abilities surviving the stress test), while certainly requiring replication and further investigation, can be discussed in the context of stress resilience mechanisms, which leaves open several promising opportunities for future research in this field.

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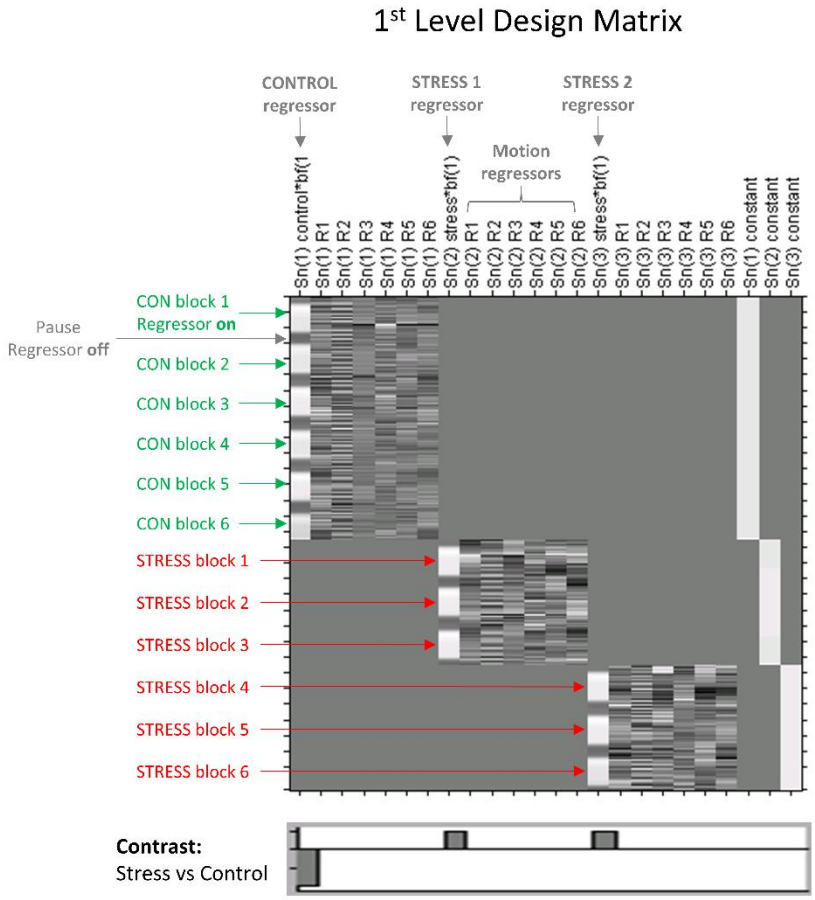
Supplement: Table of Content

Supplement Study 1.

Supplement Study 2.

Supplement 1-1

Details fMRI analysis



Supplement Figure SF1-1. Figural description of the first level design matrix. We included one control regressor modelling the onsets and duration of the 40 sec active control task blocks and two stress regressors modelling the onsets and duration of the 40 sec active stress task blocks. In addition, six motion regressors were included as covariates of no interest.

Supplement 1-2

Additional Saliva Cortisol Reactivity Measures

Instead of calculating the area under the curve with respect to increase (AUCi), other cortisol reactivity measures are currently considered to index saliva cortisol reactivity to, or recovery from an acute stressor (e.g. Bendezú & Wadsworth, 2017; Lewis et al., 2018; Miller et al., 2018). To confirm our current results, we additionally computed (1) individual baseline-to-peak values and (2) the difference between the group-peak S5 and pre-stress baseline S2, both indicating individual stress-related cortisol increase, as well as (3) the difference between S6 and S5, indicating cortisol recovery. For completeness and transparency, we repeated all correlational analyses with the new parameters. Please find all additional measures, as well as their correlations with HCC in Supplement Table ST1-1.

The analyses seem to confirm our previous results regarding HCC correlations with acute cortisol reactivity, indicated by (1) individual baseline-to-peak values and (2) Delta S5-S2, see Supplement Table ST1-1. Interestingly, cortisol recovery (3) correlated positive with HCC, indicating that the decrease in saliva cortisol from S5 to S6 was higher in individuals with higher hair cortisol. Note, although common in the literature, calculating the delta between S6 and S5 is a simplification of the complex and dynamic recovery process, since cortisol recovery was not the main interest of this study. Nevertheless, a careful consideration of cortisol recovery as the amount of decrease from S5 to S6 is warranted when interpreting the current results. In addition, we again found significant neuro-endocrine intercorrelations of stress-related dACC activity with saliva cortisol reactivity (positive) and recovery (negative). See Supplement Table ST1-1 for a detailed correlational matrix, including additional cortisol metrics as well as inter-correlations of cortisol and other reactivity markers.

Supplement Table ST1-1
Correlation matrix of all HCC correlations and inter-correlations of all acute stress reactivity markers, including additional cortisol measures.

	Correlation coefficients (*r*)									
	(1a)	**(1b)**	**(1c)**	**(1d)**	**(2)**	**(3a)**	**(3b)**	**(3c)**	**(4)**	**(5)**
(1a) AUCi	1									
(1b) baseline-to-peak	.87**	1								
(1c) Reactivity (S5-S2)	.87**	.96**	1							
(1d) Recovery (S6-S5)	-.54**	-.74**	-.69**	1						
(2) HR reactivity	-.08	.05	.03	-.14	1					
(3a) dACC activity	.38*	.41*	.37*	-.43**	-.11	1				
(3b) Insula (r) activity	.22	.26	.24	-.32	-.14	.52**	1			
(3c) Insula (l) activity	.12	.18	.15	-.20	-.15	-57**	.74**	1		
(4) MDBF reactivity	.03	.07	.22	-.26	-.15	.26	.13	.05	1	
(5) HCC	-.47**§	-.37*	-.43*	.37*	.31	-.51**§	-.28	-.35	-.31	1
	Descriptive Statistics									
M	129.42	5.14	3.18	-1.83	10.09	.58	1.70	1.52	1.12	6.41
SD	246.44	6.53	6.38	2.23	15.36	.57	.68	.69	1.55	4.43
Min	-269.62	-1.14	-3.96	-7.79	-58.78	-.87	.10	-.32	-2.13	.23
Max	956.71	34.67	33.42	1.21	29.87	1.85	3.23	2.94	6.75	17.62

Note. AUCi = Area under the curve with respect to increase; dACC = Dorso-anterior cingulate cortex; HCC = hair cortisol concentration; HR = Heart Rate; MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol samples. *p < .05; **p < .01; §*p*-value passing the Bonferroni-corrected *p*-value as described in chapter 2.3.2 of the main manuscript.

Supplement 1-3

Sex Differences in Acute Stress Reactivity and HCC

As some studies report sex differences in acute stress reactivity (Kudielka & Kirschbaum, 2005) we provide an informative supplement on (1) possible sex differences in all stress reactivity markers, (2) possible differences in cortisol time course in male and female participants, and (3) the exploration of sex differences in hair cortisol and the association with acute AUCi response.

(1) To check for sex differences in acute stress reactivity, we conducted two-sample *t*-tests in all reactivity measures. Interestingly, there were no significant differences, see Supplement Table ST1-2 for results. Note, that cautious interpretation of these results is recommended due to large variations in sample sizes (n_{women} = 12, n_{men} = 26).

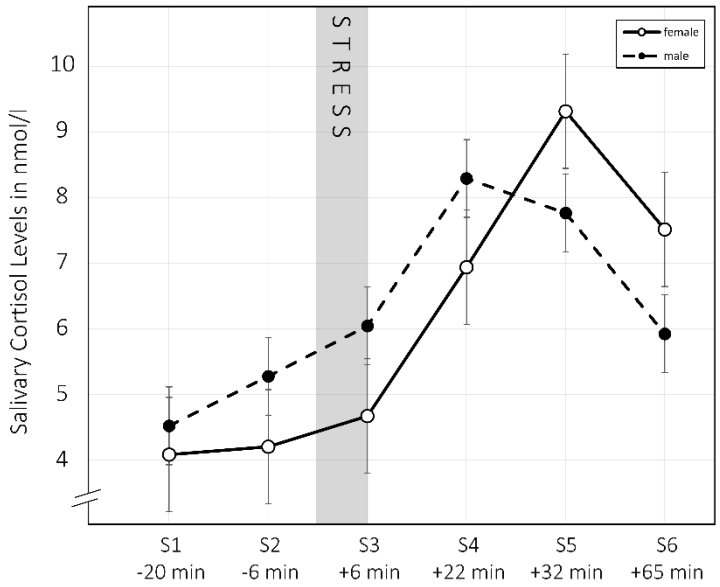
Supplement Table ST1-2
Exploratory comparison of male and female stress responses on all stress reactivity markers.

Stress Reactivity Markers		male		female			
		N	*M (SD)*	*N*	*M (SD)*	*t* (*df*)	*p*
(1) AUCi reactivity		26	132.10 (224.94)	12	123.63 (298.75)	0.10 (36)	.923
(2) MDBF reactivity		27	0.95 (1.80)	12	1.50 (0.65)	-1,02 (37)	.313
(3) dACC activity		27	0.64 (0.52)	11	0.43 (0.68)	1.04 (36)	.305
(4) Insula activity	L	27	1.63 (0.68)	11	1.73 (0.70)	1.41 (36)	.165
	R	27	1.77 (0.76)	11	1.53 (0.42)	1.00 (36)	.322
(5) HR reactivity		23	10.17 (17.83)	10	9.91 (8.02)	0.14 (31)	.966

Note. AUCi = Area under the curve with respect to increase; dACC = dorsal anterior cingulate cortex; HCC = Hair cortisol concentration; HR = Heart rate; MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol samples.

(2) As in some studies cortisol responses to acute stress have been shown to be sensitive to sex effects, we conducted an rmANOVA with time (6 levels) as a within-subject factor and sex (2 levels) as between-subject factor. Again, post-

hoc analyses of contrast focused on the samples immediately before (S1, S2) and after (S3, S4) the stress protocol. Analyses confirmed the significant main effect of time $F(5, 180) = 15.56$, $p < .001$, partial $\eta^2 = .30$ (Greenhouse-Geisser corrected for lacking sphericity, $\varepsilon = .43$), indicating a statistically significant difference in cortisol concentration before (S2) and approximately 22 minutes (S4) after stress induction, $F(1, 36) = 40.07$, $p < .001$, partial $\eta^2 = .53$, as well as 32 minutes after stress induction (S5), $F(1, 37) = 20.70$, $p < .001$, partial $\eta^2 = .37$ (see Figure 1-2A and Table 1-1 for means and standard deviations). We did not observe a significant main effect of sex, $F(1, 36) = 0.01$, $p = .922$, or a significant sex by time interaction, $F(5, 180) = 1.07$, $p = .352$ (Greenhouse-Geisser corrected, $\varepsilon = .43$). Note, that cautious interpretation of these results is recommended due to large variations in sample sizes ($n_{women} = 12$, $n_{men} = 26$).

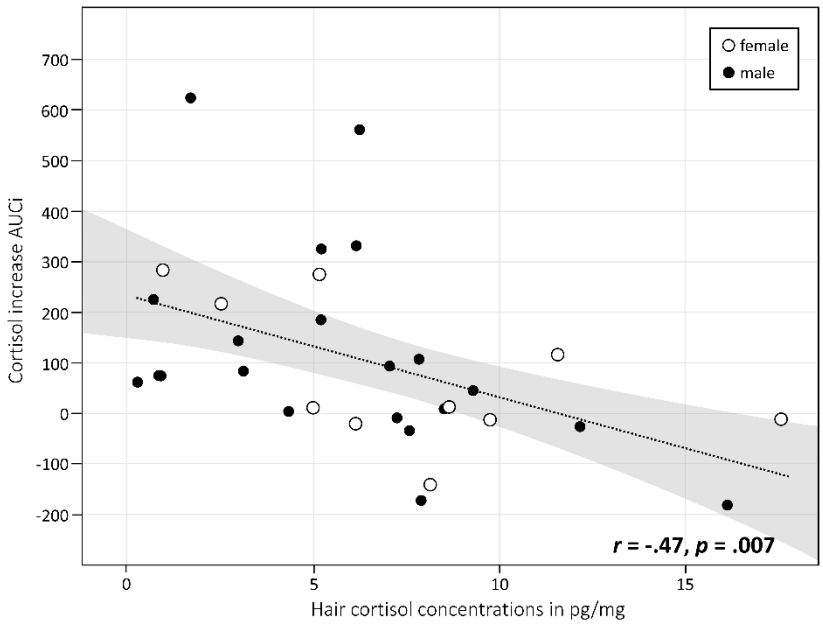


Supplement Figure SF1-2. Sex-specific time courses of cortisol concentrations are depicted for visualization only. Note, there was no significant main effect of sex, or a sex by time interaction. Error bars represent standard error of the mean.

(3) Oral contraceptives are known to influence both, HCC as well as acute cortisol reactivity (Stalder et al., 2017). Since all our female participants were under contraceptive medication, our present correlational finding of HCC with acute

cortisol reactivity might be influenced by a confounding effect of oral contraceptive intake. We therefore, first (a.), checked for sex differences in HCC, and second (b.), provided a sex-specific depiction of the scatterplot from Figure 1-4A to see if the correlational finding was driven mainly by one group (see Supplement Figure SF1-3). Considering our small sample size, we refrained from further subgroup-analyses, since large variations in sample sizes (n_{women} = 12, n_{men} = 26) would certainly limit the interpretability and validity of resulting findings. In addition, we (c.) controlled for sex in a partial correlation of HCC and saliva cortisol AUCi.

a. Interestingly, absolute HCC levels were *higher* in females (M = 7.97, SD = 4.91) than in males (M = 5.59, SD = 4.03), although a two-sample t-test revealed no significant sex differences, $t(33) = 1.54$, $p = .133$. Hence, a blunting effect of OC use seems rather unlikely for the present sample.
b. The sex-specific scatterplot reveals no hints of an underlying sex effect driving the correlational finding of HCC with AUCi, see Supplement Figure SF1-3. Hence, we assume that the significant negative correlational finding in the full sample goes beyond the mere oral contraceptive effects in female participants. Nevertheless, we certainly cannot rule out that oral contraceptives affect this correlation to some extent. Further studies are warranted to examine in detail if and to what extend oral contraceptive use influences different HPA markers and their interaction.
c. The partial correlation of HCC and saliva cortisol AUCi was still significant when controlling for sex, $r(28) = -.46$, $p = .011$.



Supplement Figure SF1-3. Sex-specific depiction of correlational results: HCC correlates negative with stress-related cortisol increase (AUCi). AUCi = Area under the curve with respect to increase.

Supplement 1-4

No Differences of Cortisol Responders and Non-Responders on Other Stress Reactivity Markers than Cortisol

Classification of cortisol responders based on a baseline-to-peak increase of > 1.5 nmol/l (Miller et al., 2013) resulted in a responder rate of 73.7 %. Interestingly, responders and non-responders did not differ in their stress reactivity on affective, neural or heart rate level, see Supplement Table ST1-3 for mean comparisons. Hence, it is assumed that the non-responders did experience stress to some extent, regardless of the missing cortisol response.

Supplement Table ST1-3
Exploratory comparison of cortisol responders and non-responders on other stress reactivity markers.

Stress Reactivity Markers		Responder		Non-Responder			
		N	*M (SD)*	*N*	*M (SD)*	*t* (*df*)	*p*
(1) AUCi reactivity		28	185.93 (256.94)	10	-28.79 (117.74)	2.53 (36)	.016*
(2) MDBF reactivity		27	1.00 (1.40)	12	1.00 (1.89)	-0.71 (37)	.483
(3) dACC activity		27	0.61 (0.55)	11	0.50 (0.63)	0.55 (36)	.588
(4) Insula activity	L	27	1.50 (0.74)	11	1.59 (0.57)	-0.39 (36)	.698
	R	27	1.65 (0.67)	11	1.82 (0.74)	-0.69 (36)	.492
(5) HR reactivity		24	10.30 (17.27)	9	9.54 (9.43)	0.13 (31)	.902
(6) HCC		24	5.61 (3.95)	10	8.41 (5.28)	-1.70 (32)	.155

Note. AUCi = Area under the curve with respect to increase; dACC = dorsal anterior cingulate cortex; HCC = Hair cortisol concentration; HR = Heart rate; MDBF = German Mood Questionnaire; S1-S6 = saliva cortisol samples. *p < .05; **p < .01.

In addition we included responder-class as a between-subject factor in the rmANOVA on MDBF scores, resulting again in a significant main effect of time, $F(5, 180) = 4.17$, $p = .015$ (Greenhouse-Geisser corrected, $\varepsilon = .49$), but no main effect of responder class, $F(1, 36) = 0.001$, $p = .975$, or time*responder class interaction, $F(2.28, 82.21) = 1.33$, $p = .256$.

Supplement 1-5

Correlational Analyses on Maximal Sample Size

As described in chapter 2.3.2, missing data from several participants in each of the different stress reactivity measures resulted in $n = 31$ participants for whom data on most stress reactivity markers were available, e.g. cortisol, MDBF, and fMRI data. In a first step, correlational analyses with HCC were performed in this subsample (case-wise procedure) and results are reported in the manuscript, chapter 2.3.2. In a second step, we performed correlational analyses on the largest sample size possible for each reactivity marker (pair-wise procedure) to maximize the sample size and power of calculations. Note, that results did not change remarkably, see Supplement Table ST1-4. Please note that according to the Bonferroni correction for multiple testing, correlations were considered significant when passing the following adjusted $p_{corr} < (.05/6) = .008$.

Supplement Table ST1-4
Correlational analyses of all stress reactivity markers with HCC (pair-wise procedure).

Stress Reactivity Markers		**Descriptive Statistics**	**Correlational coefficients (*r*)**
		N_{max} (for HCC correlation)	HCC
(1) AUCi reactivity		34	-.49**§
(2) MDBF reactivity		33	-.21
(3) dACC activity		32	-.51**§
(4) Insula activity	L	32	-.35
	R	32	-.28
(5) HR reactivity		26	.31

Note. AUCi = Area under the curve with respect to increase; dACC = dorsal anterior cingulate cortex; HCC = Hair cortisol concentration; HR = Heart rate; MDBF = German Mood Questionnaire; SMA = supplementary motor area. *$p < .05$; **$p < .01$; §p-value passing the Bonferroni-correction as described in Supplement 1-5.

Supplement 1-6

Exploratory Correlational Analyses of HCC with Other Cluster Activation and Deactivation

For the sake of completeness and transparency and to advance science, we extracted the mean subject-specific *z*-values of all clusters showing significant activation or deactivation in the main effect contrast 'stress vs. control' using the MarsBaR toolbox (http://marsbar.sourceforge.net). Note, that significant clusters of the salience network, (i.e. the anterior Insula and the dACC) are excluded here, since they are part of our correlational hypothesis and therefore reported in the main text, chapter 2.4.2.

Supplement Table ST1-5
Exploratory correlational analyses of HCC with all clusters showing significant activation or deactivation in the contrast 'stress vs. control', exclusive significant clusters of the salience network, (i.e. anterior Insula, dACC).

Brain structure	**Correlational coefficients (*r*)**
	HCC *N* = 31
Activation (stress versus control)	
Inferior parietal cortex	-.08
	-.01
Superior frontal gyrus	-.17
	.15
Supplementary motor area (SMA)	-.24
Inferior frontal gyrus (pars opercularis)	-.18
	-.24
Inferior temporal gyrus	-.22
Cerebellum	.02
	.14
	-.25
Inferior frontal gyrus (pars triangularis)	-.16
	.08
Brainstem	-.17
Fusiform gyrus	-.01

Middel occipital gyrus	-.06
Deactivation (control versus stress)	
Medial frontal gyrus	-.03
Posterior cingulate cortex	-.16
Angular Gyrus	.19
	.08
Rolandic operculum	-.35
	-.44*
Cerebellum	.09
Amygdala	-.20
	-.15
Precentral gyrus	-.49**
Middle temporal gyrus	-.04
	-.01

Note. L = left hemisphere; R = right hemisphere; M = medial; MNI = Montreal Neurological Institute. *$p < .05$; **$p < .01$ (uncorrected).

Supplement 2-1

ROI Analysis of Emotion Regulation

To further investigate stress effects on reappraisal network activity, we conducted a region of interest (ROI) analysis using 13 ROIs from a meta-analysis of 48 neuroimaging studies of reappraisal (Buhle et al., 2014). Using the MarsBaR toolbox (http://marsbar.sourceforge.net), we centered eleven spheres (6 mm) on activation peaks from the reappraisal vs. emotional baseline contrast and two 4 mm spheres on the bilateral amygdalae from the emotional baseline vs. reappraisal contrast reported in Buhle et al. (2014), see Supplement Table ST2-1 for MNI coordinates. We extracted the mean parameter estimates of the contrast reappraise_negative vs. view_negative for each ROI and compared cluster activity between groups using two-sample *t*-tests to test for stress-related differences in emotion regulation network activity. According to the Bonferroni correction for multiple testing, comparisons were considered significant when passing the following adjusted $p_{corr} < (.05/13) = .004$. Note that no significant group differences in reappraisal ROIs emerged (see Supplement Table ST2-1), mirroring the results of the whole brain analysis in chapter 3.4.2.

Supplement Table ST2-1.
ROI analysis of a stress effect on Reappraisal: mean parameter estimates of the contrast reappraise_negative vs. view_negative.

ROI		**MNI coordinates**			**SG**		**CG**			
		x	*y*	*z*	*N*	*M* (*SD*)	*N*	*M* (*SD*)	*t*(*df*)	*p*
Inferior frontal gyrus	R	60	24	3	40	0.41 (0.58)	39	0.44 (0.47)	-0.19 (77)	.852
Middle frontal gyrus	R	51	15	48	40	0.41 (0.62)	39	0.64 (0.81)	-1.44 (77)	.154
Medial frontal gyrus	R	9	30	39	40	0.15 (0.24)	39	0.16 (0.18)	-0.30 (77)	.766
Anterior cingulate gyrus	L	-3	24	30	40	0.45 (0.48)	39	0.45 (0.46)	-0.05 (77)	.960
Superior frontal gyrus	L	-9	12	69	40	0.79 (0.56)	39	0.72 (0.44)	0.58 (77)	.565
Middle frontal gyrus	L	-33	3	54	40	0.35 (0.35)	39	0.35 (0.29)	0.02 (77)	.985
Anterior insula	L	-36	21	-3	40	0.41 (0.38)	39	0.36 (0.33)	0.59 (77)	.554
Inferior frontal gyrus	L	-42	45	-6	40	0.41 (0.59)	39	0.41 (0.67)	0.02 (77)	.986
Superior temporal gyrus	R	63	-51	39	40	0.16 (0.48)	39	0.37 (0.53)	-1.86 (77)	.067
Angular gyrus	L	-42	-66	42	40	0.47 (0.48)	39	0.55 (0.57)	-0.71 (77)	.477
Middle temporal gyrus	L	-51	-39	3	40	0.30 (0.31)	39	0.29 (0.29)	0.21 (77)	.835
Amygdala	R	30	-3	-15	40	-0.02 (0.17)	39	0.002 (0.17)	-0.47 (77)	.643
Amygdala	L	-18	-3	-15	40	0.04 (0.32)	39	0.08 (0.34)	-0.55 (77)	.581

Note. CG = Control Group; L = left hemisphere; MNI = Montreal Neurological Institute; R = right hemisphere; ROI = Region of interest; SG = Stress Group;

Supplement 2-2

Table of Scan*STRESS*-C fMRI Results

Supplement Table ST2-2
MNI coordinates of peak voxels and corresponding T and $p_{\_FWE}$ values of activation clusters that show significant group differences when contrasting the two phases of the ScanSTRESS-C, i.e. [stress vs. control] for the Stress Group and [control1 vs. control2] for the Control Group.

Brain structure		MNI coordinates			Statistical values		
		x	y	z	*k*	Mean *T*	$p_{\_FWE}$
Activation (stress versus control)							
Inferior parietal cortex	R	36	-52	54	6349	12.20	< .001
	L	-42	-40	44	9226	12.00	< .001
Inferior frontal gyrus	R	48	12	24	1729	11.36	< .001
	L	-46	10	30	2128	11.29	< .001
Supplementary motor area	M	4	20	48	725	10.37	< .001
Inferior temporal gyrus	R	50	-54	-10	536	9.78	< .001
Precentral gyrus	R	26	-2	50	1032	9.42	< .001
Anterior insula cortex	R	32	22	0	408	9.16	< .001
	L	-30	28	0	210	6.77	< .001
Cerebellum	L	-28	-70	-46	42	7.89	< .001
	L	-14	-44	-46	67	6.52	< .001
Brainstem	L	-6	-25	-6	12	6.35	< .001
	R	6	-26	-4	11	5.89	< .001
Dorsoanterior cingulate cortex	M	-2	6	26	26	5.63	< .001
Deactivation (control versus stress)							
Posterior cingulate cortex	M	-2	-44	34	988	9.05	< .001
Angular Gyrus	L	-54	-64	30	566	8.92	< .001
	R	56	-60	38	118	7.62	< .001
Superior frontal gyrus	L	-18	32	56	2043	8.74	< .001
	R	14	42	52	26	6.52	< .001
Middle temporal gyrus	R	62	-10	-20	70	6.82	< .001

	L	-60	-10	-18	39	6.23	< .001
Middle frontal gyrus	L	-4	24	-20	57	6.47	< .001
Posterior insula cortex	L	-36	-18	20	26	6.20	< .001
	R	40	-14	8	37	5.77	< .001
Cerebellum	R	30	-78	-32	28	5.64	< .001

Note. L = left hemisphere; R = right hemisphere; M = medial; *k* = cluster size in voxels; MNI = Montreal Neurological Institute.

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Erklärung

gemäß § 6 Absatz 2 g) und gemäß § 6 Absatz 2 h) der Promotionsordnung der Fachbereiche 02, 05, 06, 07, 09 und 10 vom 04. April 2016

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Akademischer Hintergrund

Mai 2021	Promotion in der Psychologie an der Johannes Gutenberg Universität; Titel der Dissertation: "Characterizing the Dynamic Multilevel Stress Response and ist Influence on Cognitive Emotion Regulation“
Seit April 2019	Postgradueller Weiterbildungsstudiengang zur Psychologischen Psychotherapeutin (Schwerpunkt: Verhaltenstherapie) Poliklinische Institutsambulanz der Johannes Gutenberg-Universität Mainz
Seit Oktober 2016	Doktorandin der Abteilung Klinische Psychologie und Neuropsychologie Psychologisches Institut, Johannes Gutenberg-Universität Mainz
September 2017	Master of Science Psychologie an der Johannes Gutenberg-Universität Mainz: Note 1.0
	<u>Prüfungsfächer:</u> Forschungsmethoden und Diagnostik Klinische Psychologie und Neuropsychologie Rechtspsychologie Anwendungsorientierte Kognitionswissenschaften AOW Psychologie Ätiologische Modelle psychischer Störungen Arbeitspsychologie Nebenfach: Sportpsychologie
	<u>Hochschullehrer*innen:</u> Prof. Dr. Stefan [redacted], Prof. Dr. Michael [redacted], Prof. Dr. Heiko [redacted], Prof. Dr. Wolfgang [redacted], Prof. Dr. Axel [redacted],

Prof. Dr. Günter [redacted], Dr. Daniel [redacted], Prof. Dr. Martin [redacted], Prof. Dr. Thomas [redacted], Dr. Paul [redacted], Prof. Dr. Michèle [redacted]

September 2013 – Januar 2014 — Auslandsstudium an der Universität Haifa, Israel
Inhaltlicher Schwerpunkt: Konfliktpsychologie und Terrorismus

September 2014 — Bachelor of Science Psychologie an der Johannes Gutenberg-Universität Mainz: Note 1.3

Prüfungsfächer:
Biologische Psychologie
Methodenlehre
Allgemeine Psychologie
Entwicklungs- und Sozialpsychologie
Persönlichkeitspsychologie und Diagnostik
Arbeits-, Organisations- und Wirtschaftspsychologie
Gesundheitspsychologie
Klinische Psychologie
Nebenfach: Sportwissenschaften

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Prof. Dr. Mitja [redacted], Prof. Dr. Stefan [redacted], Prof. Dr. Gerd Gottfried [redacted], Prof. Dr. Wolfgang [redacted], Prof. Dr. Thomas [redacted], Prof. Dr. Ella [redacted], Prof. Dr. Günter [redacted], Prof. Dr. Daniel [redacted], Prof. Dr. Randolph [redacted], Prof. Dr. Malte [redacted], Prof. Dr. Thomas [redacted], Prof. Dr. Inge [redacted], Prof. Dr. Perikles [redacted], Prof. Dr. Gerhard [redacted], Prof. Dr. Michèle [redacted]

Publikationen:

Sandner, M., [redacted], [redacted], & [redacted] (2021). Cognitive emotion regulation withstands the stress test: An fMRI study on the effect of acute stress on distraction and reappraisal. *Neuropsychologia*, 157, 107876.

Sandner, M., [redacted], [redacted], [redacted], [redacted], [redacted], & [redacted] (2020). Investigating individual stress reactivity: High hair cortisol predicts lower acute stress responses. *Psychoneuroendocrinology.* https://doi.org/10.1016/j.psyneuen.2020.104660

[redacted], **Sandner, M.,** & [redacted] (2019). Script-based Reappraisal Test - Introducing a new paradigm to investigate the effect of reappraisal inventiveness on reappraisal effectiveness. *Cognition & Emotion.* https://doi.org/10.1080/02699931.2019.1663153

[redacted], [redacted], **Sandner, M**., [redacted], [redacted], [redacted], & [redacted] (2020). Perceived threat modulates inhibitory performance. *Emotion.* https://doi.org/10.1037/emo0000746

Konferenzbeiträge

Sandner, M., [redacted], [redacted], & [redacted] (2019, September). Investigating Cognitive Emotion Regulation in the Face of Stress. Poster at the 5th international resilience symposium, Mainz, Germany.

Sandner, M., [redacted], [redacted], & [redacted] (2019, August). Investigating Cognitive Emotion Regulation in the Face of Stress. Poster at the 49th annual conference of the International Society of Psychoneuroendocrinology, ISPNE, Milan, Italy.

Sandner, M., [redacted], [redacted], & [redacted] (2019, August). Investigating Emotion Regulation under Stress. Talk at the 49th annual conference of the International Society of Psychoneuroendocrinology, ISPNE, Milan, Italy.

Sandner, M., [redacted], [redacted], & [redacted] (2018, September). Does chronic stress immunize against acute stress exposure? - Hair Cortisol predicts blunted reactivity to an acute stressor. Poster at the 4th international resilience symposium, Mainz, Germany.

Sandner, M., [redacted], [redacted], & [redacted] (2018, September). Does chronic stress immunize against acute stress exposure? - Hair Cortisol predicts blunted reactivity to an acute stressor. Poster at the 48th annual conference of the International Society of Psychoneuroendocrinology, ISPNE, Los Angeles, California, USA.

Sandner, M., [redacted], [redacted], & [redacted] (2018, July). Does chronic stress immunize against acute stress exposure? - Hair Cortisol predicts blunted reactivity to an acute stressor. Poster at the 11th FENS Forum of Neuroscience, Berlin, Germany.

Sandner, M., [redacted], & [redacted] (2017, September). Characterizing the dynamic stress response - Adaptation and validation of an in-MR paradigm to investigate various stress effects in humans. Poster at the 47th annual conference of the International Society of Psychoneuroendocrinology (ISPNE), Zurich, Switzerland.