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LIVING AND COPING WITH STRESS: NEUROIMAGING FINDINGS IN THE FRAMEWORK OF AN ONGOING LONGITUDINAL STUDY

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ACE	Adverse Childhood Experiences
ADHD	Attention-Deficit / Hyperactivity Disorder
AUDIT	Alcohol Use Disorders Identification Test
BDI-II	Beck Depression Inventory
BPD	Borderline Personality Disorder
CAR	Cortisol Awakening Response
CBT	Cognitive Behavioral Therapy
CRISIS	Coronavirus Health and Impact Survey
CT	Cortical Thickness
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ELS	Early Life Stress
EMA	Ecological Momentary Assessment
EMI	Ecological Momentary Intervention
ENIGMA	Enhancing Neuro Imaging Genetics through Meta-Analysis
EPI	Echo-planar imaging
FTND	Fagerström Test for Nicotine Dependence
FWE	Family-wise error
HRF	Hemodynamic response function
IAPS	International Affective Picture System
IFG	Inferior Frontal Gyrus
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Aged Children
LS	Life Stress
MARS	Mannheim Study of Children at Risk
MDD	Major Depression Disorder
MEI	Mannheimer Elterninterview
MEL	Munich Event List
MFG	Middle Frontal Gyrus

MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
OFC	Orbitofrontal Cortex
PFC	Prefrontal Cortex
PTSD	Posttraumatic Stress Disorder
rt-fMRI-NF	Real-time functional MRI neurofeedback
SCID-5-CV	Structured Clinical Interview for DSM-5
SE	Standard Error
SPM12	Statistical parametric mapping version 12
SSD	Stop-Signal Delay
SSRT	Stop-Signal Reaction Time
SST	Stop-Signal Task
TSST	Trier Social Stress Test
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex
VR	Virtual Reality
WFU	Wake Forrest University

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1 INTRODUCTION

Major life events, traumatic experiences, and prolonged stress exposure are among the most prominent risk factors for the onset and persistence of long-lasting physical and mental health impairments, including coronary heart diseases and autoimmune diseases, but also major depression disorder (MDD) and post-traumatic stress disorder (PTSD). In one of the initial studies assessing aversive experiences in childhood, nearly 50 % of around 14,000 adults retrospectively reported the experience of at least one traumatic event in childhood from one of seven categories, such as psychological, physical or sexual abuse, parental violence, or living with a household member suffering from a mental health disorder (Felitti et al., 1998). Moreover, the exposure to such adverse childhood experiences (ACE) was associated with an increased risk for alcoholism, drug abuse, obesity, and a variety of further physical diseases in adulthood, such as cardiovascular or other chronic diseases. Replicating and expanding those findings, ACEs were found to account for almost one third of lifetime psychiatric disorders in a representative sample of over 50,000 adults across 21 countries (Kessler et al., 2010). Besides direct consequences on an individual's physical and mental health (Hughes et al., 2017), ongoing stress load during development is related to socio-economic disadvantages, lower social integration, decreased professional success (Liu et al., 2013), unhealthy lifestyles (Monnat & Chandler, 2015), and overall reduced life expectancy (Rod et al., 2020). Remarkably, a cohort study investigated the association of the experience of ACEs and suicide attempts in almost 18,000 adults (Dube et al., 2001). While the prevalence for a suicide attempt was 3.8 % in the general population, the risk for an attempted suicide was 2 to 5 times increased in those with previous exposure to ACEs, indicating ACEs as a tremendous risk factor for suicidal ideation and attempts. Moreover, the impact of prolonged stress exposure is not only limited to an individual itself, but affects families and

communities, and is to a certain degree transgenerational (Berlin et al., 2011; Dixon et al., 2008; Pears & Capaldi, 2001; Youssef et al., 2018).

The exact pathways linking life stress in early years to the development of major health impairments are not yet fully understood. However, over the last years several important factors have been identified. For instance, the crucial role of the timing of a stressor, the type, and the frequency of its occurrence have been highlighted in the development and persistence of mental health impairments (Croft et al., 2019; Herzog et al., 2020; Schalinski et al., 2016). In addition, in recent years, an overwhelming amount of neuroimaging studies pointed to structural and functional alterations in distinct brain areas, such as the prefrontal cortex (PFC), the amygdala, or the hippocampus, as mediating factors in the association of stressful experiences and mental health impairments (Bick & Nelson, 2016; Herzog & Schmahl, 2018).

This thesis aims at further investigating the specific impact of stressful life events at distinct developmental stages on structural brain alterations and its association with mental health exemplary described for MDD in the framework of the Mannheim Study of Children at Risk (MARS), an ongoing epidemiological at risk cohort study following its participants since birth. Moreover, we provide novel evidence for the importance of adaptive coping to an unforeseen stressor. Therefore, we will first briefly outline the impact of stressful events at different developmental stages on behavior and brain maturation, with a focus on the PFC. Given its critical role in socio-affective and emotional processing, the PFC is widely considered to be particularly vulnerable to early life adversities (Heim & Binder, 2012; Teicher et al., 2003). Furthermore, it is one of the latest brain regions to fully develop, with a postnatal maturation in gray matter volume until late adolescence (Andersen & Teicher, 2008; Gee & Casey, 2015; Lenroot & Giedd, 2006), and thus especially sensitive to environmental adversities occurring in early years (Lupien et al., 2009).

However, given the high prevalence of adverse childhood experiences, the question arises why some individuals do not suffer from those traumatic experiences neither immediately nor in the long run, while others show long lasting mental and physical health impairments. The characterization and impact of individual risk and protective factors, such as coping strategies, personality traits, or social integration is a main focus in trauma research (Holz et al., 2019; Traub & Boynton-Jarrett, 2017). Therefore, in the second part of this thesis, we will introduce emotion regulation and cognitive control as coping mechanisms in response to unforeseen stress, their association with early life adversities, and their underlying neural pathways.

We, as humans, are characterized by lifelong ongoing development and maturation. Starting during gestation and continuing postnatally during infancy probably the most tremendous but typical neuro-developmental changes occur within likely the shortest period (Lupien et al., 2009; Pfefferbaum et al., 1994; Vasung et al., 2019). Afterwards, childhood and adolescence as a transition phase into adult life are marked with ongoing growth not only in physical constitution but also in socio-affective behavior (Arnett, 2001; Crone & Dahl, 2012; Kilford et al., 2016; Somerville, 2013). Exposure to critical life events or ongoing stress is consistently shown to alter these normal developmental trajectories (Felitti et al., 1998; Lupien et al., 2009). A fundamental understanding of critical time periods in which development is particularly sensitive to stress exposure is therefore inevitable (Heim & Binder, 2012). The following section outlines the consequences of stress exposure from infancy to adolescence on behavior, psychopathology, and neural outcomes.

1.1 Early life stress

Exposure to perinatal and early life stress (ELS) in infancy is critically involved in the onset of a variety of physical health impairments (Crouch et al., 2019), such as an increased risk for cardiovascular diseases (Bellis et al., 2015; Farr et al., 2015), diabetes (Basu et al.,

2017), asthma (Gilbert et al., 2015) or even cancer (Morton et al., 2012). ELS includes a variety of different noxious events, predominantly focusing on environmental adversities such as growing-up in poverty, the experience of chronic family disharmony, the sudden loss of a relative, or parental psychopathology, but include also severe traumatic events, with an immediate direct impact on an individual, such as physical or sexual abuse or maltreatment (Crouch et al., 2019; Finkelhor et al., 2013). Moreover, ELS marks a risk factor for abnormal development with regard to stress-related hormonal functioning (Yam et al., 2015). For instance, children exposed to maternal depression within the first year after birth showed elevated levels of cortisol segregation in response to an acute stressor (Dreger et al., 2010). Furthermore, interpersonal trauma experienced up to the age of 2 years, such as physical or emotional abuse, neglect, or witnessing of maternal partner violence, led to reduced cognitive development at the age of 8 years compared to those without a history of traumatic experiences in infancy (Enlow et al., 2012).

Remarkably, the risk for developing a mental disorder is up to twice as high for children exposed to ELS. Around 45 % of all childhood-onset psychiatric disorders and around 30 % of later-onset disorders are associated with ELS, with a marked difference in the onset, progression, and treatment response in exposed patients. Even more, the experience of ELS is associated with a markedly increased risk for suicidality in later life (Angst et al., 2011; Cowan et al., 2016; Turecki et al., 2012; Wanner et al., 2012). For instance, in a nation-wide Danish sample, Ostergaard investigated the relationship of six different adversities in infancy, including low social class, severe marital discord, overcrowding, paternal criminality, maternal mental disorder, and placement in foster care, and Attention-Deficit/Hyperactivity Disorder (ADHD) in childhood (Ostergaard et al., 2016). Early life adversity was strongly related to ADHD diagnoses in later life, with a dose-depended

relationship, indicating the more adversity in infancy the higher the risk for developing ADHD before the age of 20 years.

1.1.1 Effect of early life stress on brain structure and function

A variety of studies reported abnormal brain development related to the exposure to early life adversities. For instance, several studies investigated the consequences of early life institutionalization, often being associated with early psychosocial and physical neglect (Sheridan et al., 2012), on brain maturation. Gray matter volume reductions were consistently found in adopted adolescents previously institutionalized compared to adoptees who were never institutionalized (Mehta et al., 2009; Sheridan et al., 2012). Moreover, the authors found distinct alterations in the hippocampus and the amygdala. In addition, diminished emotion regulation abilities and increased amygdala volumes in children who were adopted to the United States compared to those who were growing up with their birth family was reported (Tottenham et al., 2010). Besides the consequences of institutionalization, further studies addressed effects of further dimensions of ELS on brain alterations. For instance, Hanson investigated the impact of poverty and socio-economic disparities on brain maturation from infancy into early childhood in a sample of 77 children (Hanson et al., 2013). The authors found reductions in overall gray matter volume, especially in frontal and parietal regions, in those children who grew up under low socioeconomic conditions. Interestingly, children living in low-income environments were characterized by delayed brain maturation from infancy to early childhood, indicating that low socioeconomic environments may alter typical brain development.

So far, animal models demonstrated alterations in the PFC in degus and rhesus macaques, which were separated from their parents in infancy (Helmeke et al., 2009; Rilling et al., 2001; Sanchez et al., 2001). Moreover, Yuan et al. reported long-term effects of early

life stress on the prefrontal brain in squirrel monkeys (Yuan et al., 2021). Between the ages of 17 to 27 weeks female monkeys in the experimental condition were separated from their group once a week for one hour. Around 9 years later, those monkeys which were exposed to early life stress were characterized by hyper-connectivity between parts of the PFC and subcortical structures, including the amygdala and hippocampus, indicating long-lasting effects of stress in infancy on the PFC. However, evidence for the impact of ELS on PFC alterations in human samples remains limited. For instance, in 37 healthy adolescents early life stress up to the age of 5 years and ongoing stress between the ages of 14 and 17 years were assessed via parent report (Tyborowska et al., 2018). In addition, structural brain scans were conducted at the ages of 14 and 17 years. Brain changes from 14 to 17 years were highly associated with early life stress, indicating that more negative life events in infancy resulted in greater brain volume decreases, especially in prefrontal, frontal, and temporal regions, but also in subcortical structures. In contrast, pubertal stress was not related to gray matter alterations. In line with these results, our own group reported significantly decreased orbitofrontal cortex (OFC) volumes in young adults who were at risk of poverty during infancy (Holz et al., 2015), suggesting sustained effects of early life adversity reaching until adulthood, and indicating prefrontal regions as particularly sensitive to environmental threat.

1.2 Stress during childhood and adolescence

Childhood and adolescence are characterized by typical developmental changes in self-perception and socio-affective behavior, such as moving from parents to peers, a higher sensitivity to peer influence, or altered emotional reactivity (Crone & Dahl, 2012; Kilford et al., 2016; Somerville, 2013). Given the high numbers of traumatic experiences obtained in children and adolescents, this transition time is widely considered as a highly sensitive period for environmental adversities (Hauser et al., 2011; Lupien et al., 2009). In a representative German sample of adolescents aged 14 years and older, physical abuse was reported by 2.8 %

and sexual abuse by 1.9 % of the participants (Hauser et al., 2011). In addition, 6.6 % of all participants reported severe emotional neglect, whereas 10.8 % reported severe physical neglect, underlining a critically high prevalence of severe events in youths.

1.2.1 Effect of stress during childhood and adolescence on brain structure and function

Several studies demonstrated the detrimental impact of childhood-onset maltreatment on functional and structural brain alterations. Here, we briefly outline findings on the impact of childhood and adolescence adversities with a focus on prefrontal regions. For instance, Hart reported hyperactivation of the ventromedial PFC (vmPFC) and the anterior cingulate cortex (ACC) during an emotion processing task in adolescents who experienced childhood maltreatment before the age of 12 years in comparison to children previously not exposed to maltreatment (Hart et al., 2018). Adolescent girls who were exposed to socio-economic disadvantages between the age of 5 years until the age of 16 years showed altered neural responses in the medial PFC during a reward task, with these alterations mediating the association between socio-economic disparities and current depressive symptoms at the age of 16 years (Romens et al., 2015). Gray matter volume reductions in the OFC, the ACC, and the hippocampus were found in patients with child-abuse related complex PTSD compared to healthy controls (Thomaes et al., 2010). Self-reported emotional maltreatment before the age of 16 years was linked to volume reductions in the dorsomedial PFC (dmPFC) in adult patients with internalizing disorders (van Harmelen et al., 2010). Adults who were exposed to self-reported childhood trauma were characterized by diminished gray matter volume in the cingulate gyrus and showed an increased cortisol awakening response (CAR) compared to non-exposed individuals, suggesting an altered stress-sensitivity associated with childhood maltreatment (Lu et al., 2013).

Besides its impact on prefrontal regions, several further regions are consistently linked to childhood-onset stress. For instance, childhood neglect and abuse at the ages of 11 to 13 years was a significant predictor of alterations in the amygdala and hippocampal volume (Herzog et al., 2020; Teicher et al., 2018). Similar results were found by Mielke who investigated brain alterations and its interplay with oxytocin in women with or without the experience of physical or sexual abuse before the age of 18 years (Mielke et al., 2018). For trauma-exposed individuals the authors report different relationships between cortisol levels and structural brain alterations in the amygdala, the hypothalamus and the nucleus accumbens, all regions which have been previously linked to childhood maltreatment.

Together with the ongoing typical neurodevelopmental changes, the above-mentioned findings demonstrate that the timing of environmental stress is crucial in the development of stress-related alterations. Moreover, these findings point to sensitive periods in development, but also to distinct brain regions which are both particular vulnerable to threatening events and ongoing stress exposure (Gee & Casey, 2015). However, most of the studies outlined above used retrospectively collected data on childhood adversities (Anda et al., 2006; Crouch et al., 2019; Felitti et al., 1998), which are highly susceptible for recall-bias. A recall-bias indicates that test subjects remember past events or experiences as better or worse, or as less or more frequent than they actually were (Coughlin, 1990), thereby decreasing the validity of the data. Moreover, the exact timing of an adverse event, especially during early life stages, for instance in infancy, is difficult to access. If there is no acceptable information provided by the parents or documented for instance in medical records or court files, infantile amnesia often prevents adults to remember certain events which happened prior to the age of 3 years (Alberini & Travaglia, 2017). Therefore, prospectively collected longitudinal data, especially for early life stress, is particularly needed to overcome these limitations.

1.3 Impact of stress on internalizing symptoms

The experience of ELS is consistently associated with the development, persistence, severity, and treatment-responsivity in internalizing disorders, particularly in MDD (Chapman et al., 2004; Nanni et al., 2012; Nelson et al., 2017). A recent meta-analysis reported that childhood maltreatment was associated with a 2.66 times increased risk for developing MDD in adulthood, and 46 % of MDD patients experienced any form of childhood adversity (Nelson et al., 2017). In patients with exposure to childhood maltreatment the onset of MDD was around four years earlier than in those without a history of adverse childhood experiences (Nelson et al., 2017). Moreover, maltreated patients had an increased risk for developing chronic depressive symptoms (Nanni et al., 2012), and were characterized by heightened resistance to treatment (Nanni et al., 2012; Nelson et al., 2017). The following section briefly introduces MDD, followed by neurobiological findings and their interplay with ELS.

1.3.1 Prevalence and clinical characteristics of MDD

MDD is one of the most prevalent and severe mental disorders in the general population. Around 8.1 % of the adult German population currently suffer from MDD, with women being more affected than men, and an overall lifetime prevalence of 11.6 % (Busch et al., 2013). MDD is characterized by an ongoing dysregulation of affective states, a lower mood, and a reduced interest in previously positively experienced leisure activities or social interactions (American Psychiatric Association, 2013). Besides those cardinal symptoms, further symptoms include a lack of motivation, alterations in eating or sleeping behavior, difficulties in concentrating, and sustained reduced self-esteem (American Psychiatric Association, 2013). Moreover, those affected frequently report suicidal ideation, whereas suicide attempts are documented in 15 to 40 % patients with a diagnosis of MDD (Chen & Dilsaver, 1996; Riihimäki et al., 2014; Sokero et al., 2005), causing MDD to be one of the

most lethal mental disorders (Ösby et al., 2001). In addition, around 50 to 85 % of those affected experience one or more relapses (American Psychiatric Association, 2013; Burcusa & Iacono, 2007), indicating the far reaching consequences of MDD.

1.3.2 Neural underpinnings of internalizing symptoms

Several meta-analyses investigated the neural underpinnings related to MDD. For instance, Kempton reported smaller volumes of the orbitofrontal cortex, the hippocampus, the basal ganglia, and the thalamus in MDD patients compared to healthy controls (Kempton et al., 2011). In addition, the authors found differences in hippocampal volume between those participants experiencing a current depressive episode compared to those in remission. Besides that, Bora found overall gray matter volume reductions in the rostral ACC (Bora et al., 2012). Furthermore, the authors reported significant volume reductions in the dorsolateral and dorsomedial PFC in patients who previously suffered from multiple depressive episodes. Similar results were found by Lai, demonstrating alterations of the ACC when comparing MDD patients to healthy adults (Lai, 2013). Finally, in medication-free MDD patients, gray matter reductions in prefrontal and limbic regions were found compared to healthy controls (Zhao et al., 2014). While gray matter volume is a composite measure derived from the product of cortical thickness (CT) and surface area (Raznahan et al., 2011), alterations in those distinct cortical measures have been additionally linked to MDD. For instance, the largest ever worldwide study conducted in the framework of the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) project compared anatomical data of 2,148 MDD patients to almost 8,000 healthy controls at different ages (Schmaal et al., 2017). They found that in adult MDD patients the OFC was thinner than in healthy controls. In addition, adolescents with MDD were characterized by reduced overall surface area, and had distinct regional reductions, particularly in frontal regions, such as the medial OFC and the superior frontal gyrus.

1.3.3 Neural pathways linking internalizing symptoms to early life stress

So far, studies investigating the association of ELS, MDD, and structural and functional brain alterations are sparse. For instance, Saleh investigated the impact of ELS on neurocognitive performance and brain alterations in a sample of 64 medication-free depressed adults compared to 65 healthy controls (Saleh et al., 2017). Participants reported the experience of 19 traumatic events during childhood and adolescence up to the age of 17 years. Exposure to severe family conflicts, emotional trauma, and sexual abuse in childhood and adolescence predicted the diagnosis of MDD. Moreover, increased ELS was related to diminished performance during neuropsychological testing. Interestingly, decreased OFC and caudate volumes were related to increased ELS in childhood and adolescence. In a recent prospective study, Weissman reported decreased hippocampal and amygdala volumes in adolescents previously exposed to childhood adversities. Further, those volumetric reductions mediated the relationship between childhood adversities and an increasing depressive symptomatology two years later, suggesting a neural pathway between ELS and MDD (Weissman et al., 2020).

Taken together, several studies so far highlighted the detrimental impact of ELS at different developmental stages on the brain. Moreover, a robust link between ELS and MDD has been demonstrated with mounting evidence pointing to a dramatically increased risk for MDD, early disease onset, prolonged persistency, and diminished treatment-response as a consequence of ELS. However, the underlying neurobiological pathways connecting ELS and MDD remain largely unknown. Therefore, the first part of this thesis aims to further investigate the relationship of ELS, MDD, and brain alterations.

In the second part of this thesis, we will introduce two distinct coping mechanisms, emotion regulation and cognitive control, in response to acute and ongoing stress, briefly discuss their relationship to early life adversities, and describe their biological underpinnings.

1.4 Coping with stress

The ability to adapt to new and stressful environments starts very early in life and continues to be inevitable across the life span. However, while some coping mechanisms are considered to be adaptive to certain adversities, others may appear successful in the first place, but are followed by negative consequences in the long run. In addition, the question arises why some individuals cope better with adverse events while others do not. The following section gives a brief overview of different coping mechanisms, their association with early life stress, and associated neural underpinnings, with this thesis focusing on emotion regulation and inhibitory control.

1.4.1 Emotion regulation

A core feature in response to environmental stress or threatening events is an adequate, adaptive, and fast regulation of emotional states. Emotion regulation hereby refers to the ability to react to and modulate emotional states (Gross, 2015; Holley et al., 2017) and encompasses a variety of affective processes, such as cognitive reappraisal or emotional suppression. Cognitive reappraisal is considered as an adaptive emotional coping strategy to decrease negative emotions. It comprises the ability to actively reinterpret an emotion-eliciting situation to change its emotional impact (Goldin et al., 2008). It is thereby considered as an antecedent-focusing strategy, starting before the complete activation of emotional responses has begun (Gross, 1998, 2002). Emotional suppression, however, describes an approach to hide, stop or redirect emotion-expressive behavior, and thus is considered as a response-focused strategy, stepping in when an emotional response has been fully generated (Goldin et al., 2008; Gross, 2002).

Experimental studies found that cognitive reappraisal has a positive impact on affect regulation, it is associated with increased experience of positive emotions in everyday life,

and overall better mental health conditions (Garnefski & Kraaij, 2006; Garnefski et al., 2004; Gross, 2002, 2015; Hu et al., 2014; Moore et al., 2008). Therefore, cognitive reappraisal is widely considered as an adaptive emotion regulation strategy. In contrast, emotional suppression is associated with increased emotional arousal and internalizing symptoms, impairments in cognitive performance, and heightened negative affect in daily life (Compare et al., 2014; Eastabrook et al., 2014; Gross & John, 2003; Haga et al., 2007; Katana et al., 2019; Nezlek & Kuppens, 2008; Schafer et al., 2017). Excessive use of emotional suppression is thus considered as maladaptive.

1.4.1.1 Emotion regulation, stress, and psychopathology

Difficulties in emotion regulation have been documented in a wide range of stress-related mental disorders, such as MDD, PTSD, or borderline personality disorder (BPD; Aldao et al., 2010), but are also highly linked to early life adversities (Poole et al., 2017, 2018; Repetti et al., 2002). For instance, in young adults prenatally exposed to cocaine, difficulties in emotion regulation have been reported (Richardson et al., 2019). In a sample of 262 children and adolescents, maltreatment was related to greater use of emotion suppression (Weissman et al., 2019). Further, in trauma exposed adults, excessive use of emotion suppression was positively associated with psychopathology (Amstadter & Vernon, 2008). In addition, increased use of suppression was associated with higher depression scores (Joormann & Gotlib, 2010; Kudinova et al., 2018; Sai et al., 2016). In contrast, frequent usage of cognitive reappraisal was linked to reduced risk for MDD in children who were exposed to parental psychopathology (Kudinova et al., 2018). Moreover, the habitual use of cognitive reappraisal moderated the impact of early life adversities on chronic stress in adults (Kalia & Knauft, 2020), suggesting the protective role of cognitive reappraisal between early life and adult stress.

1.4.1.2 Neural components of emotion regulation

From a neural perspective, several meta-analyses indicate the important role of the PFC in emotion regulation (Davidson et al., 2000; Ochsner et al., 2002). Together with the amygdala, the PFC interacts to form a connected system which mediates adaptation to stress and emotion. Parts of the PFC are hereby widely considered as top-down-regions which regulate the amygdala in response to threatening or aversive stimuli (Davidson et al., 2000). Therefore, adaptive emotion regulation strategies, such as cognitive reappraisal, are associated with an increased activity in the inferior frontal gyrus (IFG), ventrolateral PFC (vlPFC), dorsolateral PFC (dlPFC), medial PFC (mPFC), and reduced amygdala reactivity to negative stimuli (Gross, 2015).

Given these rather general neural findings, alterations in neural activity related to emotion regulation have been well documented with regard to early life adversities. For instance, childhood poverty has been found to be related to reduced PFC activity in an emotion regulation task in adults (Kim et al., 2013; Liberzon et al., 2015). In contrast, in children and adolescents with a history of maltreatment, higher activity of the PFC and lower involvement of the amygdala during an affective reappraisal task were related to lower risk for depression (Rodman et al., 2019), suggesting the protective role of adequate usage of reappraisal against environmental stress.

1.4.2 Inhibitory control

Inhibitory control is, aside from working memory and cognitive flexibility, a core domain of executive functions (Diamond, 2013; Morgan & Lilienfeld, 2000) and refers to the ability to voluntarily stop or suppress an undesirable, inappropriate or irrelevant behavior, attention or thought (Casey et al., 2002; Durston et al., 2002). Appropriate inhibitory control enables us to resist various temptations in daily life, such as eating too much chocolate or to

keep on a boring task, even if there would be more pleasant alternatives (Diamond, 2013). Inhibitory control is suggested to have an extended developmental progression (Constantinidis & Luna, 2019; Kochanska et al., 2001), i.e., starting early in life, infants are already able to inhibit or delay unwelcomed behavior, possibly representing an appropriate adaption to external expectations, such as waiting for meals or playing with toys of siblings (Kochanska, 1997; Morasch & Bell, 2011). Continuing in early childhood until adolescence, adequate inhibitory control becomes more and more important to fulfill the general requirements of kindergarten, school, and society. Laboratory studies assessing inhibitory control performance report a rapid improvement from infancy to childhood and adolescence (Constantinidis & Luna, 2019), with findings also showing the beneficial use of early inhibitory control trainings. For instance, preschoolers received a training to promote executive functions, including aspects of self-regulation, memory, and attention over a period of up to two years in their classroom from their regular teachers (Diamond et al., 2007). Compared to children who received a different curriculum, including the same academic teaching, but without specific training on inhibitory control, children in the training group performed significantly better in two standardized laboratory tasks. In turn, a better task performance was positively related to academic success, indicating the importance of adaptive inhibitory control (Diamond et al., 2007).

1.4.2.1 Inhibitory control, stress, and psychopathology

Difficulties and impairments in inhibitory control across the life span are often linked to impulsivity and are highly prevalent in mental disorders, but also associated with early life adversities (Lukito et al., 2020; McTeague et al., 2016; Piguet et al., 2016). In a meta-analysis Lipszyc and Schachar investigated the association of inhibitory control during the stop-signal task (SST), a widely used task to assess response inhibition, and 10 different mental disorders, including ADHD, schizophrenia, and MDD (Lipszyc & Schachar, 2010). Impaired SST

performance, as reflected by the stop-signal reaction time (SSRT), was prominent in several mental disorders, including ADHD, schizophrenia, or obsessive-compulsive disorders, whereas only little evidence was found for inhibitory control deficits in MDD or anxiety disorders. With regard to early life adversities, young children prenatally exposed to methamphetamine showed reduced performance during inhibitory control (Derauf et al., 2012). Children who experienced early life maltreatment had significantly more difficulties in inhibitory control compared to children without a history of maltreatment (Cowell et al., 2015). Adopted children who have been to multiple foster homes performed significantly worse during an inhibitory control task than non-adopted children and adopted children who have been to only one prior foster home (Lewis-Morrarty et al., 2007). In addition, adolescents who were adopted in infancy showed diminished performance in a cognitive control task (Mueller et al., 2010). Furthermore, early life institutionalizing was associated with behavioral deficits during inhibitory control in adults (Chugani et al., 2002). Furthermore, in a longitudinal study Anzman-Frasca followed a cohort of 192 girls from the ages of 7 to 15 years and investigated the adaptive role of inhibitory control on psychosocial, cognitive, and weight outcomes (Anzman-Frasca et al., 2015). Increased levels of inhibitory control, as assessed via parental report at the participants' age of 7 years, predicted lower levels of depressive symptoms, higher self-reported self-competence, and better performances in school between the ages of 9 to 15 years, indicating the beneficial usage of inhibitory control on well-being across childhood and adolescence.

1.4.2.2 Neural components of inhibitory control

From a neural perspective, inhibitory control has been linked to a functional and structural involvement of a fronto-basal-ganglia circuit including the IFG, the middle and medial frontal gyrus, and the basal ganglia (Aron, 2007; Aron et al., 2004; Verbruggen & Logan, 2008). For instance, several functional MRI studies using the SST found that the IFG

was highly activated when the initial stop process was successful, representing efficient inhibitory control (Verbruggen & Logan, 2008). Moreover, previous studies found impaired stop performances in participants with lesions to the basal ganglia, indicating a substantial role of additional subcortical contribution in inhibitory control (Verbruggen & Logan, 2008).

With regard to early life stress, several studies found an association between neural alteration and stress exposure. For instance, functional connectivity abnormalities were found in adolescents with a history of childhood abuse compared to non-exposed adolescents (Hart et al., 2018). Our own group found decreased neural responses in several frontal areas, including the IFG and the ACC during inhibitory control in young adults who were prenatally exposed to tobacco smoke (Holz et al., 2014). In contrast, in adults exposed to childhood maltreatment less inhibition of the right IFG by the dorsal ACC was associated with better inhibitory control, suggesting inhibitory control and its underlying neural pathways as potentially adaptive to environmental stress (Elton et al., 2014).

Besides the long-lasting relationship between early life stress and inhibitory control alterations, a recent study documented the impact of acute stress on inhibitory control (Roos et al., 2017). Using the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a widely applied instrument to induce acute social stress, Roos found diminished inhibitory control in participants previously exposed to acute stress (Roos et al., 2017). These results highlight the importance of adaptive coping particularly under stress.

In summary, emotion regulation and inhibitory control are well investigated coping strategies, with mounting evidence highlighting parts of the PFC to be particularly involved. Difficulties in coping strategies are highly prevalent in mental disorders and have been consistently linked to ELS. However, most of the studies described above investigated coping in response to chronic or acute stress, with the predictive value in response to future stressors of those strategies remaining largely unknown. Therefore, this thesis further aimed at

predicting stress burden due to an unprecedented naturalistic event by using neural activity elicited during emotion regulation and inhibitory control assessed prior to this event.

1.5 Hypotheses

1.5.1 Long-term effects of early adversity on brain morphology

Long-term effects of life stress on distinct components of brain morphology, including cortical volume, CT, and surface area have been investigated in many studies using retrospectively collected data on early adversities. Given this approach, recall-bias of participants cannot be ruled out, indicating the necessity for prospectively collected measures. In contrast, given the unique longitudinal design of our study following adults since birth, we previously reported OFC volume alterations in young adults who were at risk for childhood poverty (Holz et al., 2015), with the impact of life stress on CT and surface area remaining unknown. Therefore, study 1 addresses the impact of adverse life events prospectively collected in regular intervals on orbitofrontal CT and surface area in a sample of 190 adults who underwent structural MRI at the age of 25 years. We expect decreased orbitofrontal CT and surface area in those, who were previously exposed to increased adverse events.

1.5.2 The crucial role of timing

Previous findings highlighted the importance of critical time periods in which distinct neural regions are particularly sensitive to environmental stress. However, longitudinal studies following children from birth into adulthood are sparse, but particularly needed to investigate those sensitive periods. Our longitudinal study design thereby enables us to quantify stressful life events at different developmental stages, particularly in infancy, childhood, and adolescence (study 1) and investigate their specific impact on brain morphology in adulthood. Given previous findings, we expect brain alterations in those who were exposed to heightened stressful events in infancy.

1.5.3 Early life stress, the brain, and mental health

So far, the underlying pathways connecting the experience of childhood adversities and internalizing symptoms to brain alterations are poorly understood. Therefore, we additionally aimed at investigating the underlying pathways between ELS, brain alterations, and MDD symptoms, by testing whether the effect of ELS on structural alterations in adults is mediated by depressive symptoms throughout young adulthood. Depressive symptoms were assessed at the participants' age of 22 and 23 years using the Beck Depression Inventory (BDI-II; Hautzinger et al., 2006). We expected MDD symptoms in young adults to mediate the relationship between ELS and morphological aberrations and thereby provide a potential pathway linking early LS, depressive symptoms, and brain alterations.

1.5.4 Coping under stress

Effective coping with unknown, threatening, and fearful events is highly important, with findings indicating difficulties in coping mechanisms to be highly prevalent in those exposed to ACEs and in those with mental disorders. However, the predictive value of neural activity on stress burden has not yet been extensively investigated, especially with regard to a naturally occurring, acute stressor. In study 2, we investigated two coping strategies, namely emotion regulation and inhibitory control, and explored their usage during a naturally occurring stressor, i.e., the COVID-19 pandemic. In early 2020 the novel SARS-CoV-2 virus caused a global health crisis, affecting physical and mental health, and led to unprecedented restrictions in daily life around the world. Therefore, appropriate coping in response to such a stressor is inevitable to overcome the distinct challenges caused by the pandemic. We expected that higher emotion regulation and inhibitory control assessed prior to the pandemic would predict lower stress burden during the COVID-19 crisis. Moreover, we hypothesized that emotion regulation in order to overcome perceived stress burden would be more

important at the beginning of the first and second wave of the crisis when participants were confronted with direct threat due to high infection rates and increased death numbers, whereas inhibitory control would become increasingly important to cope with the ongoing socio-economic uncertainties during the pandemic in the summertime when infection rates decreased and social contact restrictions eased.

2 EMPIRICAL STUDIES

2.1 Study 1: The Long-Term Impact of Early Life Stress on Orbitofrontal Cortical Thickness

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2.1.1 Abstract

Early adversity has been related to brain structure alterations and to an increased risk of psychiatric disorders. The orbitofrontal cortex is a key region for emotional processing, with structural alterations being described in several mental disorders. However, little is known about how its cortical thickness is affected by the long-term impact of life stress at different developmental stages. The present study aimed to investigate the effect of life stress during infancy, childhood and adolescence on cortical thickness alterations in the orbitofrontal cortex and on psychopathology in 190 adults of an ongoing prospective cohort study. Chronic stressful life events were assessed in regular intervals. Participants rated depressive symptoms at the ages of 22 and 23 years. Morphometric data were collected at the participants' age of 25 years. Chronic life stress during infancy were associated with reduced cortical thickness in the right orbitofrontal cortex and increased depressive symptoms. Moreover, the impact of chronic life stress during infancy on orbitofrontal cortex thickness was partially mediated by depressive symptoms in adulthood, suggesting an interplay of early life stress, psychopathology and cortical thickness alterations. Our findings highlight the long-term impact of early life stress on an affective core brain structure and psychopathology later in life.

2.1.2 Introduction

Adverse childhood experiences (ACE) are highly prevalent among individuals suffering from mental disorders (Kessler et al., 2010). ACEs often refer to traumatic experiences such as sexual and physical abuse or neglect (Felitti et al., 1998), but also encompass exposure to chronic life stress (LS), including growing up in poverty, experiencing long-term parental conflicts or witnessing severe illness of a relative (Finkelhor et al., 2013). Exposure to LS is associated with an increased risk of psychopathology, such as Major Depressive Disorder (MDD; Carr et al., 2013) and somatic illness (Felitti et al., 1998), underlining the crucial role of LS in the behavioral and biological development of children and adolescents (Cicchetti & Carlson, 1989; Pechtel & Pizzagalli, 2011).

Several studies have highlighted the impact of the timing of LS on brain development and psychopathology (Andersen & Teicher, 2008; Lupien et al., 2009), with findings indicating that brain regions involved in emotional processing and with an ongoing postnatal development are particularly vulnerable to early environmental stress (Heim & Binder, 2012; Teicher et al., 2003). The prefrontal cortex (PFC) is one of the last regions in the brain to fully develop, showing a postnatal increase in gray matter and reaching its peak volume in adolescence (Andersen & Teicher, 2008; Gee & Casey, 2015). Given these neuro-developmental changes from infancy to adolescence, it is crucial to gain an understanding of critical time periods in which brain development is particularly sensitive to LS (Gee & Casey, 2015). Indeed, a variety of neuroimaging studies have reported detrimental effects of early LS on the PFC, particularly in orbitofrontal regions (De Brito et al., 2013; Hanson et al., 2010; Holz et al., 2015; Saleh et al., 2017). For example, a smaller volume of the orbitofrontal cortex (OFC) was found in physically abused children (Hanson et al., 2010). Our own group demonstrated significantly decreased OFC volumes in young adults who had been at risk of poverty during infancy (Holz et al., 2015), suggesting persistent effects of early life adversity.

Moreover, the OFC is a key region in emotion regulation, reward processing and motivational processing (Davidson et al., 2000; Rubia, 2010), and morphometric and functional alterations have been linked to several mental disorders, such as MDD (Bremner et al., 2002; Lacerda et al., 2004; Peterson et al., 2009).

Cortical volume is a composite measure, determined by the product of cortical thickness (CT) and surface area (Raznahan et al., 2011). Therefore, a sole focus on volume alterations may underestimate the complexity of neural development (Sowell et al., 2004). CT and surface area follow different developmental trajectories, representing two genetically distinct morphometric properties (Panizzon et al., 2009), which might be affected by LS at different developmental stages in distinct ways. CT has been found to have a major impact on overall cognitive and behavioral functioning (Shaw et al., 2006), with CT alterations being frequently reported in several mental disorders such as MDD (Peterson et al., 2009; Wagner et al., 2012).

Moreover, there is growing evidence of an impact of ACEs on CT in children and adolescents, with an emphasis on the importance of early life stress. For example, 6-9-year-old children who had been exposed to prenatal maternal depression showed significantly reduced CT in the right frontal lobe, including superior and medial orbitofrontal regions, which in turn was linked to increased affective instability (Sandman et al., 2015). In early institutionalized children, CT reductions were found in prefrontal, parietal and temporal areas, and mediated the association of deprivation with impulsivity and inattention (McLaughlin et al., 2014). A higher parental educational level predicted increased CT in the right ACC and the left superior frontal gyrus in typically developing children aged 4-18 years, which suggests a potential impact of chronic adverse living conditions on CT development (Lawson et al., 2013). Furthermore, sexual or physical abuse in childhood was associated with more conduct disorder and hyperactivity symptoms and reduced CT in a wide range of frontal structures, including the anterior cingulate (ACC), the superior frontal gyrus, and the anterior

orbitofrontal cortex in children (Kelly et al., 2013). Similar results were found in adolescents aged 13-20 years, replicating the detrimental impact of abuse on CT alterations in the ventromedial PFC and the lateral OFC (Busso et al., 2017).

Taken together, while these findings demonstrate a strong association of LS at different developmental stages with OFC structure and CT alterations in general, research investigating the long-term impact of exposure to chronic early LS on CT, and the interplay of LS, CT and psychopathology, is sparse. Thus, assessing the timing of long-term consequences of early life burden on CT might contribute to a better understanding of the neural mechanisms increasing the risk of mental disorders.

Therefore, we aimed to investigate the long-term impact of exposure to chronic LS at different developmental stages on OFC thickness. Using longitudinal data from 190 currently healthy young adults, we addressed the following: First, we investigated the long-term impact of LS during development on OFC thickness during adulthood. Chronic LS was assessed at regular intervals, beginning at the participants' age of 3 months, which allowed us to disentangle critical time periods from infancy to adolescence within one sample. In addition, we aimed to clarify whether morphological alterations are exclusive to CT or are also present in surface area. Childhood maltreatment as well as socioeconomic disparities have been previously linked to surface area changes (Kelly et al., 2013; Noble et al., 2015), with findings suggesting reduced surface area in a wide-range of regions, including temporal areas and medial orbitofrontal regions. To our knowledge, so far there are no studies focusing on OFC surface alterations and the long-term consequences of LS from infancy to adolescence. Therefore, we explored the impact of LS at different developmental stages on the OFC surface area, expecting reduced surface area associated with increased chronic LS given the previous reported studies. Second, we aimed to replicate previous findings linking early LS to an elevated risk of developing depressive symptoms in later life (Heim & Binder, 2012). Finally, we aimed to clarify the interplay of early LS, psychopathology during young

adulthood, and CT alterations. Depressive symptoms in childhood and early adolescence have been linked to an increased rate of cortical thinning in adolescence (Bos et al., 2018; Luby et al., 2016), suggesting an early and fastened CT maturation as a consequence of childhood-onset MDD with the exact pathways to remain unknown. Therefore, we aimed to test whether the effect of early LS on CT alterations in adults is mediated by depressive symptoms throughout young adulthood to provide a potential pathway linking early LS, depressive symptoms and CT changes.

2.1.3 Materials and Methods

2.1.3.1 Sample

The present investigation was conducted in the framework of the Mannheim Study of Children at Risk, an ongoing prospective study of the long-term outcomes of early psychosocial and biological risk factors following children at risk for psychopathology since birth (for more details, see Laucht et al., 2000). Initially, 384 infants were recruited from two obstetric and six children's hospitals and were included in the sample according to a three by three-factorial design (factor 1 varying the degree of obstetric complications, 0 = no risk, 1 = moderate risk, 2 = high risk; factor 2 varying the degree of psychosocial adversity, 0 = no risk, 1 = moderate risk, 2 = high risk), which resulted in an overrepresentation of infants with increased psychosocial risk factors at birth. Starting at the age of 3 months, information on physical health, life stress and psychopathology was collected prospectively up to the age of 25 years. From the initial sample, 18 participants (4.7 %) were excluded due to severe disabilities and 57 participants (14.8 %) were classified as dropouts, resulting in a final sample of 309 participants. At the age of 25 years, an extensive screening procedure, including the Structured Clinical Interview for DSM-IV (SCID-I German version; Wittchen et al., 1997), was administered by trained psychologists to assess psychiatric disorders, somatic

health status and medication level in the current sample. Thus, we included a subsample of 190 healthy adults of the initial sample who reported no current psychopathology, no somatic illness, were free of any psychotropic medication at the time of the MRI assessment and fulfilled usual MRI criteria.

2.1.3.2 Assessments

2.1.3.2.1 Life stress

Life stress was recorded using a shortened and modified version of the Munich Events List (MEL; Maier-Diewald, 1983). The interview covered several areas of chronic stressors, which were adjusted for different developmental stages. The items included stressors regarding parental socioeconomic disadvantages, negative health outcomes, and living and environmental conditions, such as long-term parental disharmony, unemployment, illness of a relative or unsatisfactory housing. Since chronic stress is characterized by the prolonged presence of adverse conditions (Miller et al., 2007; Ostiguy et al., 2009), the burden had to be present for at least 3 months to be classified as chronic LS. LS was first assessed by interviewing either both parents or the participants' mothers, starting at the participants' age of 3 months until the age of 4 years. Thereafter, chronic LS were rated by the participants' parents using a self-report version of the MEL up to the participants' age of 15 years. Starting at the 15-year assessment, participants rated chronic life events themselves. An event was noted if it occurred within one year prior to the assessment time. For each assessment wave, LS scores were computed by summing up all single items. Subsequently, separate Z-transformed stress scores were calculated for the assessment waves up to the age of 4 years, representing infancy and toddlerhood (later referred to as infancy), up to the age of 11 years, representing childhood, and up to the age of 19 years, representing adolescence (Guerra et al., 2012).

2.1.3.2.2 Depressive symptoms

Depressive symptoms according to the DSM-IV were assessed in the 190 participants using the German version of the Beck Depression Inventory (BDI-II; Hautzinger et al., 2006) at the ages of 22 and 23. Separate sum scores were calculated for each assessment wave, after which an overall Z-transformed depression score was computed by adding up the separate sum scores in order to gain a broader overview of depressive tendencies in the participants, with the two assessment waves highly correlated with each other ($r = .559$, $p < .001$). Overall, depressive symptoms did not reach clinical cut-offs.

2.1.3.3 Covariates

The results were controlled for several confounders, including gender, lifetime substance abuse (lifetime nicotine, lifetime alcohol use, frequency of lifetime cannabis intake), pre- and early postnatal obstetric adversity, given their previously reported associations with morphological alterations. In addition, we controlled for lifetime MDD diagnoses, lifetime anxiety disorder diagnoses and years of education. Details on the assessments of these variables are described in the supplement.

2.1.3.4 Anatomical data

We acquired 1 x 1 x 1 mm^3 T1-weighted high-resolution anatomical images with 192 slices covering the whole brain (matrix 256 x 256, repetition time = 2300 ms, echo time = 3.03 ms, 50 % distance factor, field of view 256 x 256 x 192 mm^3, flip angle 9°) using a 3T scanner (Magnetom TRIO; Siemens, Erlangen, Germany) with a standard 12-channel head coil.

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, Version 6.0.0, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these

procedures are described in previous publications (Fischl & Dale, 2000). In brief, this analysis suite includes several corrections, normalization, segmentation and transformation procedures before extracting CT, surface area and volume measures in defined brain regions. CT was calculated as the shortest distance between pial surface and white matter boundaries, measured in millimeters (mm). All images were visually inspected for segmentation errors after cortical reconstruction.

2.1.3.5 Statistical Analysis

All statistical data and Z-transformed results from FreeSurfer were entered into SPSS Statistics 25 (IBM, Armonk, NY) for further analysis. For the OFC morphology, a-priori defined regions-of-interest (ROI) analysis was conducted based on the Desikan-Killiany parcellation atlas (Desikan et al., 2006) separately for the left and right hemisphere, followed by an exploratory, therefore uncorrected, analysis of the whole-brain and surface area. A threshold of $p < .05$ was used for all analysis. Pearson correlations were calculated to analyze the relationship between LS and depressive symptoms, LS and OFC morphology, LS and all covariates (sex, obstetric risk, lifetime substance abuse, years of education and lifetime MDD and anxiety disorder diagnosis), and depressive symptoms and the above-mentioned covariates. Linear regression models were subsequently used to analyze the relationship between LS and OFC morphology controlling for all covariates. Total intercranial volume was used as an additional covariate when cortical volume was entered as the outcome measure. Moreover, since right and left medial parts of the OFC were regions of interest, a conservative Bonferroni correction ($p = .025$) for the two OFC hemispheres was applied; this largely did not change the results given that the right but not left OFC would still reach significance. Additional sensitivity analyses were performed to control for the robustness of significant effects. We used Cook's distance to determine outliers based on the independent variables (i.e., LS and depressive symptoms). Participants reporting extreme (more than 3

standard deviations above the mean) or highly influential values of LS or MDD were excluded. The effect of early LS on OFC thickness was additionally controlled for LS in childhood and adolescence to specify the nature of the effect. Therefore, LS in childhood and adolescence were separately entered into the linear regression model linking early LS with the right medial OFC thickness including all above mentioned covariates.

The regression-based mediation model tested considered all the above mentioned covariates using the PROCESS macro for SPSS (Hayes, 2013). To test the mediating effect of depressive symptoms on the relationship between early LS and CT, the following criteria must be fulfilled. First, an association between LS during development and CT in adulthood must be present. Second, an association between CT at the age of 25 years and depressive symptoms in young adulthood must be established. Third, an association between LS during development and depressive symptoms in young adulthood must be present. To test the significance of the indirect effect a bootstrap estimation approach with 10,000 samples providing bias-corrected confidence intervals was used. (We additionally tested a mediation model with CT alterations in adulthood as mediator linking early LS to MDD symptoms, which can be found in the supplement.)

2.1.4 Results

2.1.4.1 Sample characteristics

Sample characteristics are shown in Table 1. As expected, chronic life events at different developmental stages were significantly correlated. That is, early LS was positively linked to chronic LS during childhood ($r = .388$, $p < .001$) and adolescence ($r = .250$, $p < .001$), with chronic LS during childhood also being positively related to chronic LS in adolescence ($r = .339$, $p < .001$). Chronic LS during infancy as well as adolescence was positively related to depressive symptoms in young adulthood (infancy: $r = .234$, $p < .001$,

Figure 1; adolescence: r = .291, p < .001). One participant was classified as an outlier, reporting 26 chronic life events, which were more than three standard deviations above the mean. After excluding this outlier, the association between LS in infancy as well as adolescence and depressive symptoms remained significant (infancy: r = .256, p < .001; adolescence: r = .293, p < .001). Childhood LS was not significantly related to depressive symptoms (r = .124, p = .090). LS and depressive symptoms were not related to the covariates (see supplement).

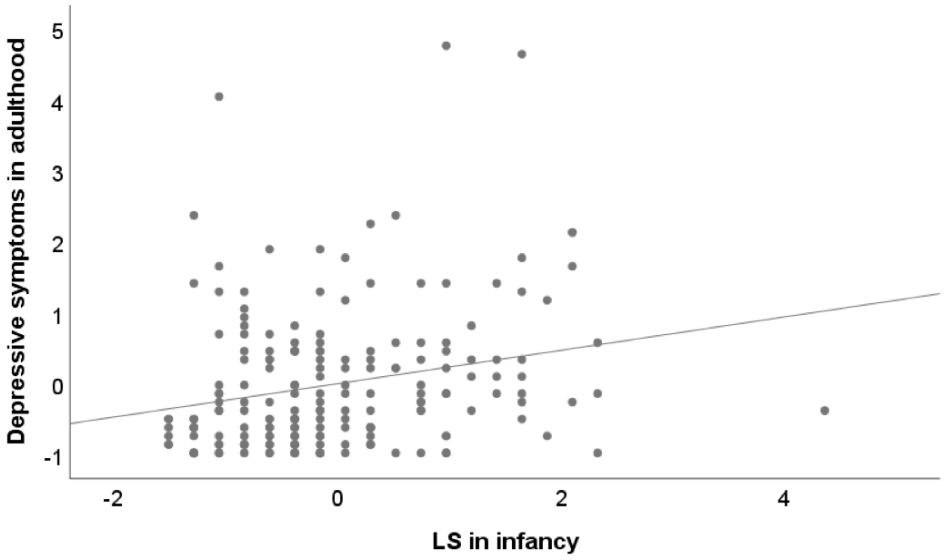

Figure 1. Scatterplot for LS in infancy and depressive symptoms in young adulthood.

Elevated exposure to early LS is related to more depressive symptoms in young adults ($r = 0.234$, $p < 0.001$). After excluding one outlier, the results remained significant ($r = 0.256$, $p < 0.001$).

Table 1. Sample characteristics

Participants, No.	190
Female sex, No. (%)	107 (56.3)
Life stress, mean (SD)	
infancy	6.68 (4.43)
childhood	5.04 (3.11)
adolescence	4.91 (2.91)
Depressive Symptoms, mean (SD)	
at age 22	4.36 (4.88)
at age 23	3.97 (4.67)
Lifetime MDD diagnoses, No. (%)	10 (5.3)
Lifetime Anxiety Disorder, No. (%)	42 (22.1)
Obstetric Risk, mean (SD)	0.95 (0.99)
Lifetime substance abuse	
AUDIT score [a], *M* (SD)	16.48 (10.83)
FTND score [a], *M* (SD)	3.21 (1.98)
Cannabis abuse, No. (%)	43 (22.6)

Abbreviation: AUDIT, Alcohol Use Disorders Identification Test; FTND, Fagerström Test for Nicotine Dependence.

[a] *Unstandardized sum scores*

2.1.4.2 Cortical thickness and life stress

Overall LS from infancy to adolescence was significantly associated with reduced CT in the right medial OFC (β = -.196, SE = .071, p = .007). In detail, we found a significant association for LS reported up to the age of 4 years and CT in the right medial OFC at the age of 25 years (β = -.274, SE = .070, p <.001, Figure 2). Moreover, LS in childhood was significantly related to CT in the left medial OFC (β = -.154, SE = .072, p = .034). There were no further regions of the OFC showing significant alterations in CT.

2.1.4.3 Sensitivity analyses

After excluding one outlier, the association between LS in infancy and right medial OFC remained significant, irrespective of the adjustment for sex, obstetric adversity, lifetime substance abuse, years of education and lifetime MDD and anxiety diagnosis (β = -.218, SE = .073, p = .003). In addition, the results remained significant after separately controlling for all covariates and LS during childhood (β = -.250, SE = .079, p = .002) and for all covariates and LS during adolescence (β = -.210, SE = .075, p = .006). In contrast, the association between LS in childhood and left medial OFC thickness was no longer significant after adjustment for sex, obstetric adversity, lifetime substance abuse, years of education and lifetime MDD and anxiety diagnoses (β = -.136, SE = .074, p = .067). Furthermore, adulthood stressors, which were reported at the age of 25 years, were not related to OFC thickness (left: β = -.070, SE = .079, p = .374; right: β = .030, SE = .077, p = .703).

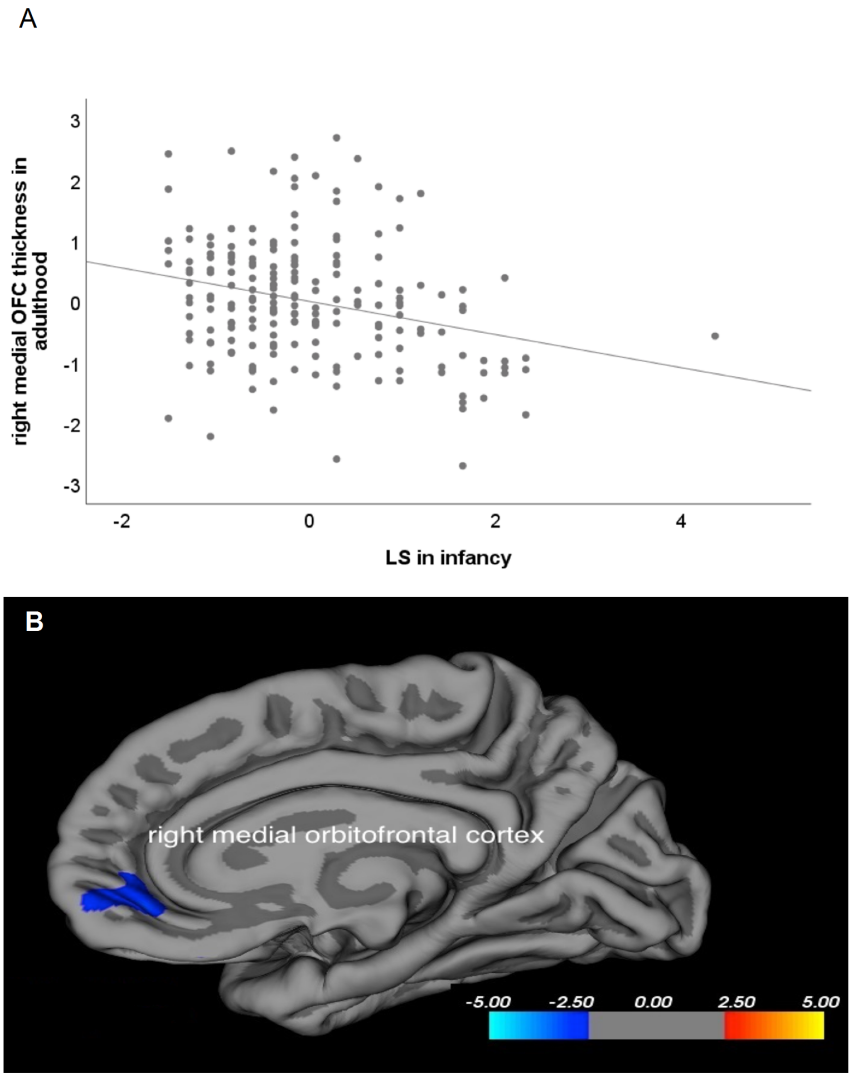

Figure 2. (A) Effects of early LS on OFC thickness. Corresponding results for the association between early LS and OFC thickness for 190 participants including the outlier (β = -0.273, SE = 0.070, p < 0.001). (B) Effects of early LS on OFC thickness. Reduced CT in the right medial OFC. Color bars represent negative log(10) P-values.

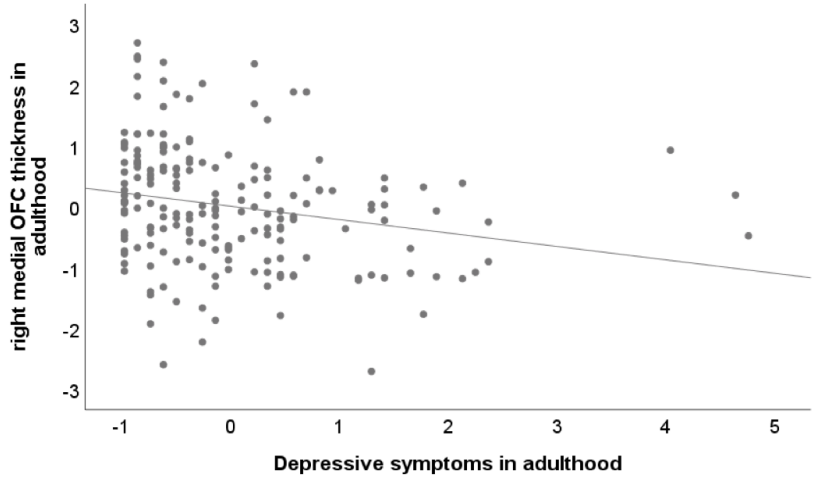

Figure 3. Scatterplot of the association between depressive symptoms and OFC thickness. Elevated depressive symptoms are associated with decreased CT in the right OFC (r = -0.221, p = 0.002).

2.1.4.4 Surface area, volume and life stress

There was no significant association between OFC surface area in both hemispheres and chronic LS in infancy, childhood and adolescence. Further, there were no significant correlations between LS and volume alterations in the OFC (all p-values > .05).

2.1.4.5 Cortical thickness and depressive symptoms

There was an inverse relationship between left and right medial orbitofrontal CT and depressive symptoms during young adulthood (left: r = -.176, p = .015; right: r = -.221, p = .002, Figure 3), indicating that a thicker OFC was linked to fewer depressive symptoms. After excluding outliers and controlling for sex, obstetric adversities, substance abuse and years of education this relationship remained significant for the right OFC (β = -.229, SE = .072, p = .002), but not for the left OFC (β = -.122, SE = .074, p = .104).

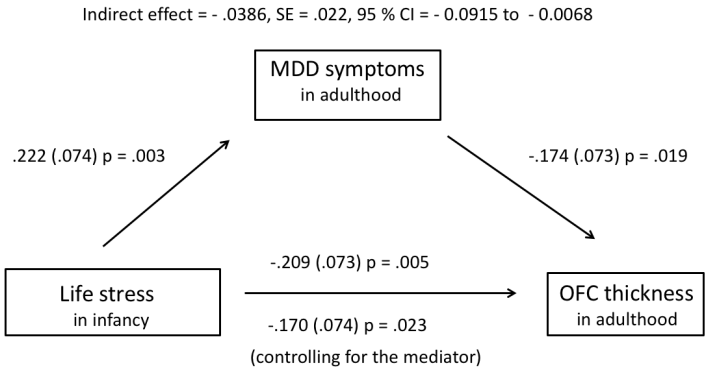

Figure 4. Mediation analysis. Path model showing an indirect path for MDD symptoms, partially explaining the impact of early LS on OFC thickness in adults. The direct path remained significant.

2.1.4.6 Mediation Analysis

There was a negative indirect effect of LS in infancy on OFC thickness in adults through depressive symptoms (indirect effect = -.0386, SE = .022, 95 % CI = -0.0915 to -0.0068), with a significant path between LS in infancy and MDD scores (β = .222, SE = .074, p = .003, Figure 4) and between depression scores and right OFC thickness (β = -.174 SE = .073, p = .019). The direct path between early LS and CT remained significant (β = -.209, SE = .073, p = .005), suggesting that the impact of LS in infancy on CT was partially mediated by depressive symptoms in young adulthood.

2.1.4.7 Whole-brain analysis

The results from the exploratory, and thus uncorrected, whole-brain analysis of significant associations for CT, surface area and volume, and LS at different developmental stages are shown in Table 2. After controlling for sex, obstetric adversities, lifetime substance abuse, lifetime MDD diagnosis, lifetime anxiety disorder diagnosis, years of education and when applicable, total intercranial volume, there were no significant associations between LS

in infancy and cortical alterations in young adults. In contrast, chronic LS in childhood was negatively correlated with the left caudal ACC ($r = -.167$, $p = .021$) and the left parahippocampal surface area ($r = -.219$, $p = .002$). In addition, LS during adolescence was inversely related to cortical thickness of the right transverse temporal lobe ($r = -.161$, $p = .026$) and the left entorhinal cortex volume ($r = -.199$, $p = .006$).

Table 2. Whole-brain analysis of significant associations between LS at different developmental stages and morphological components representing FreeSurfer output based on the Desikan-Killiany atlas

Cortical thickness		Surface area		Cortical volume	
Infancy					
		Frontal lobe			
right rostral middle frontal	r = -.146, p = .044			right pars triangularis	r = .144, p = .048
		Temporal lobe			
		left fusiform	r = .166, p = .022	left fusiform	r = .149, p = .040
		right inferior temporal	r = .162, p = .026	right inferior temporal	r = .159, p = .029
		right para-hippocampal	r = .196, p = .007		
		Cingulate			
		left posterior cingulate	r = .151, p = .037	left posterior cingulate	r = .148, p = .041
Childhood					
Cortical thickness		**Surface area**		**Cortical volume**	
		Frontal lobe			
				left caudal middle frontal	r = -.146, p = .045
		Temporal lobe			
		left para-hippocampal*	r = -.219, p = .002		
		Cingulate			
		left caudal anterior*	r = -.167, p = .021		
Adolescence					
Cortical thickness		**Surface area**		**Cortical volume**	
		Temporal lobe			
right transverse temporal*	r = -.161, p = .026	left entorhinal	r = -.147, p = .043	left entorhinal+	r = -.199, p = .006

* associations remained significant after controlling for all covariates

+ association remained significant after controlling for all covariates and total intercranial volume

2.1.5 Discussion

The present study aimed to investigate the long-term impact of childhood exposure to chronic stress at different developmental stages on structural brain alterations in healthy young adults. In the framework of an ongoing longitudinal study, our results provide evidence of the detrimental impact of exposure to chronic stress in early life on cortical thickness. Specifically, we observed reduced CT in the right OFC in individuals who experienced heightened exposure to chronic adversities during infancy and toddlerhood (up to the age of 4 years). In contrast, chronic LS in childhood and adolescence was not significantly related to CT alterations in the OFC at the age of 25 years. Moreover, we replicated previous findings linking chronic childhood adversity to elevated depressive symptoms later in life. Furthermore, reduced CT in the right OFC was associated with elevated depressive symptoms. Finally, our results revealed that the impact of early adversity on brain alterations in young adults was partially mediated by depressive symptoms.

Our findings are in line with previous studies investigating CT reductions in the OFC after exposure to adverse childhood experiences. To date, most studies have investigated the direct influence of traumatic experiences, such as abuse or separation, on an individual (Gold et al., 2016; Kelly et al., 2013). One goal of the present study was to broaden this focus to chronic stressful life events, thus emphasizing the persistent impact on the individual. These adversities, such as parental separation, unsatisfactory living conditions or poverty, are potential risk factors for the development of severe mental disorders such as MDD later in life (Greif Green et al., 2010). Using longitudinal data on stressful life events, prospectively reported by the participants' parents during early childhood, our results demonstrate a long-lasting impact of early environmental risk factors on CT development throughout the lifespan.

Cortical thickness is determined by the size, density and arrangement of neurons (Narr et al., 2005). Yet, the lifetime development of CT is not fully understood. After an increase

during infancy (Lyall et al., 2015), recent studies observed a linear and stable decline in CT in healthy participants, which begins around the age of 4 years (Ducharme et al., 2016; Forde et al., 2017). During this decline, which is often referred to as a synaptic pruning phase, unnecessary neural connections are removed, resulting in a region- and age-specific decreased CT (Forde et al., 2017; Petanjek et al., 2011). Higher-order brain regions, such as the PFC, are suggested to undergo this reorganization of neural connectivity until late adolescence and into young adulthood (Forde et al., 2017; Petanjek et al., 2011). In the present study, we demonstrated that increased exposure to adverse life events up to the age of 4 years was associated with CT reductions more than 20 years later, suggesting two potential pathways: First, while a stable cortical thinning throughout the life span is considered as normal maturation (Lemaitre et al., 2012; Petanjek et al., 2011), an accelerated decline in CT might be a consequence of prolonged exposure to early LS. Second, CT growth is reported to be completed by the age of 2 years, highlighting infancy as a critical period for brain development (Lyall et al., 2015). Therefore, adversities occurring in infancy might result in a cortical developmental delay, which may in turn result in altered neural maturation.

Moreover, in our sample, structural alterations were limited to CT, and were not found regarding surface area. CT and surface area have been shown to be characterized by distinct genetic and developmental properties (Lyall et al., 2015; Raznahan et al., 2011), with their product representing cortical volume (Raznahan et al., 2011). In line with other studies (Gold et al., 2016; McLaughlin et al., 2014), our findings suggest that chronic LS appears to distinctly affect CT and surface area, thus emphasizing the need to consider the two components separately in order to better understand their specific impact on brain plasticity and their potential contribution to mental disorders.

Alterations in cortical development are observed in several mental disorders, such as MDD (Wagner et al., 2012; Zhao et al., 2017), although the precise pathways remain poorly understood. Our results suggest that depressive symptoms might mediate the pathway

between early LS and OFC thickness. So far, several studies have investigated the effect of stressful life events on depressive symptoms, showing a robust positive association (Shapero et al., 2014). In line with the diagnostic criteria linking MDD to mood disturbances and a loss of pleasure in activities or social interaction (Wittchen et al., 1997), numerous studies reported blunted OFC activity during reward processing in MDD (Eshel & Roiser, 2010), which is one of the core neurobiological mechanisms underlying the disorder (Pechtel & Pizzagalli, 2011). Indeed, the OFC is assumed to be a key region in the top-down regulation of emotional and motivational, reward-related states (Davidson et al., 2000; Rubia, 2010). Notably, volume alterations in the OFC have been highlighted in MDD (Bremner et al., 2002; Lacerda et al., 2004), while findings on CT alterations in MDD have only recently begun to garner interest. In an ongoing population-based study of healthy elderly participants, CT reductions in a wide range of neural regions, including the OFC, were associated with subclinical depressive symptoms (Pink et al., 2017). Likewise, two studies found significant cortical thinning in the right OFC in untreated first-episode MDD patients (Han et al., 2014; Zhao et al., 2017). In a large sample with more than 2,000 MDD patients and almost 8,000 healthy controls, reduced thickness in the OFC was found in adults with MDD (Schmaal et al., 2017). Taken together, these findings highlight the relevance of CT alterations in the OFC in MDD. The nature of our longitudinal design, with psychopathology assessed prior to or concurrently with OFC thickness, allowed us to investigate a mediation model with depressive symptoms as a mediator of the relationship between early LS and OFC thickness. Elevated early LS may facilitate the onset of depressive-like behavior, such as less physical activity, less social interaction, more physiological stress reactivity, which, in turn, increase the risk for neurotoxic effects and therefore, may affect neural development. However, this pathway is not exclusive, as it may also be possible that a thinner CT in the OFC acts as a mediator (see supplement for an additional mediation model). In support of this, CT reductions in the OFC were identified as the strongest predictor of future-onset depression in

a sample of adolescent girls prospectively followed for 5 years (Foland-Ross et al., 2015), indicating CT alterations as a potential risk factor for psychopathology.

Some limitations of the current study need to be addressed when evaluating the results. First, given the two mentioned hypotheses of depression as a consequence or a precursor of OFC alterations, future studies assessing both psychopathology and CT are needed in order to clarify the exact pathway by which early LS exerts an impact on brain development and mental disorders. Second, the anatomical data described here have so far only been assessed during young adulthood, preventing us from disentangling the developmental track of the effect of LS on CT. Therefore, future prospective studies acquiring anatomical data from childhood to adulthood are necessary in order to better understand the temporal associations among LS, depressive symptoms and OFC thickness. Longitudinal studies are rare, but are particularly warranted in order to determine the exact interplay of LS, CT and depression by avoiding biased memory on the one hand and allowing predictions of developmental progress on the other hand. Third, given that CT steadily declines over time, future studies are needed to address the impact of additional confounders on CT changes, such as medication history, physical health status over time, and self-experienced severity of LS, which were not assessed in the present study. Fourth, for the MRI assessment only healthy participants without any current psychiatric or somatic disorder were included. Therefore, depressive symptoms in this sample clearly remained below a clinical cut-off. While several studies have suggested subthreshold depressive symptoms as a precursor for MDD (Fergusson et al., 2005), our results cannot be generalized to MDD patients, but may offer a potential prediction in patients. Future studies are needed to clarify the presented pathways in samples comprising healthy participants and MDD patients with a history of chronic LS at different developmental stages.

In conclusion, exposure to early LS might have a detrimental long-term impact on OFC thickness in young adults. Specifically, CT reductions in young adults are linked to

exposure to more adverse life events in infancy, with this association being partially explained by depressive symptoms. Given these findings, the present study contributes to a better understanding of the long-term effects of adverse childhood experiences on brain development and psychopathology throughout the life span, highlighting the need for early prevention to avoid stressful life events or support those at risk.

2.1.6 Supplementary Materials and Methods

2.1.6.1 Sample

Initially, 384 infants were recruited from two obstetric and six children's hospitals and were included in the sample according to a three by three-factorial design (factor 1 varying the degree of obstetric complications, 0 = no risk, 1 = moderate risk, 2 = high risk; factor 2 varying the degree of psychosocial adversity, 0 = no risk, 1 = moderate risk, 2 = high risk), which resulted in an overrepresentation of infants with increased psychosocial risk factors at birth. Starting at the age of 3 months, information on physical health, life stress and psychopathology was collected prospectively up to the age of 25 years. From the initial sample, 18 participants (4.7 %) were excluded due to severe disabilities and 57 participants (14.8 %) were classified as dropouts, resulting in a final sample of 309 participants. At the age of 25 years, an extensive screening procedure, including the Structured Clinical Interview for DSM-IV (SCID-I German version; Wittchen et al., 1997), was administered by trained psychologists to assess psychiatric disorders, somatic health status and medication level in the current sample. Thus, we included a subsample of 190 healthy adults of the initial sample who reported no current psychopathology, no somatic illness, were free of any psychotropic medication at the time of the MRI assessment and fulfilled usual MRI criteria. Of the 190 participants, 70 (36.8 %) initially had no psychosocial risk factors at birth, 67 (35.3 %)

showed moderate psychosocial risks and 53 (27.9 %) were initially classified as high risk. 72 (37.9 %) had no obstetric risk, 103 (54.2 %) had moderate obstetric risk factors and 15 (7.9 %) were classified as having high obstetric risk factors. Compared to the parent sample, including dropouts and participants, who did not take part in the MRI procedures, the MRI subsample's distribution across the psychosocial risk factors was significantly different ($\chi^2(2) = 10.11$, $p = .006$), with more participants having no psychosocial risk at birth and less participants in the high-risk group. In addition, participants also differed regarding the organic risk factors ($\chi^2(2) = 14.40$, $p = .001$), with more participants having no organic risk factors and less participants having high organic risk factors at birth.

2.1.6.2 Lifetime substance abuse

Lifetime nicotine dependence was assessed with the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) at each of the four assessment waves between the age of 19 and 25 years and added up to a total score, which was subsequently Z-transformed.

Lifetime alcohol use was measured by the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001), a self-report screening instrument to assess risky drinking behavior. The AUDIT consists of 10 items, measuring patterns of alcohol consumption, alcohol dependence and adverse outcomes of heavy drinking within the previous 12 months. Scores for each participant and each of the four assessment waves between the age of 19 and 25 years were added up to a Z-transformed total score.

Participants rated their lifetime cannabis intake by answering a standardized question regarding whether they had smoked marijuana within the last 12 months before the assessment wave at the ages of 19, 22, 23 and 25 years. A sum score of dichotomous answers (no = 0, yes = 1) was subsequently computed by adding up the values for each assessment wave.

2.1.6.3 Obstetric adversity

Obstetric adversity was assessed within a standardized parent interview conducted at the participants' age of 3 months. A sum score of obstetric risk factors was computed by adding up the presence of nine adverse conditions during pregnancy, delivery and in the early postnatal phase, such as preterm birth or low birth weight (Laucht et al., 2000).

2.1.6.4 Lifetime diagnoses of MDD and Anxiety Disorders

At the participants' ages of 2, 4, 8 and 11 years the Mannheim Parent Interview (MEI; Esser et al., 1989) was used to assess MDD and anxiety symptoms. At the age of 15 years participants and their parents were interviewed with the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS-PL, German version; Delmo et al., 2000). Beginning at the age of 19 years, mental health was assessed using the German version of the Structural Clinical Interview for DSM IV (Wittchen et al., 1997). We calculated separate lifetime MDD and anxiety scores for each participant by summing up the presence (= 1) or absence (= 0) of MDD and anxiety disorder diagnoses at each assessment wave. Out of 190 participants of the current sample, 10 participants (5.3 %) fulfilled the criteria for MDD, and 42 (22.1 %) participants fulfilled the criteria for at least one anxiety disorder at one previous time point.

2.1.6.5 Years of education

For each participant the highest school-leaving qualification was noted as years of education. 106 (55.8 %) of all participants had the highest diploma (German Abitur), which represents 13 years of school, 13 participants (6.8 %) spent 12 years to school (Fachabitur), 49 participants (25.8 %) spent 10 years at school (Realschulabschluss) and 22 participants (11.6 %) graduated after 9 years (Hauptschulabschluss).

2.1.7 Supplementary Results

2.1.7.1 LS and covariates

We found no significant relationship of early LS with obstetric risk ($r = -.123$, $p = .092$) and with lifetime substance abuse (alcohol abuse: $r = -.031$, $p = .673$; nicotine dependence: $r = .047$, $p = .520$; cannabis intake: $r = .049$, $p = .506$).

2.1.7.2 Depressive symptoms and covariates

Depressive symptoms were not related to obstetric risk ($r = -.078$, $p = .285$), lifetime substance abuse (alcohol use: $r = -.001$, $p = .991$; nicotine dependence: $r = .096$, $p = .190$; cannabis intake: $r = .068$, $p = .354$).

2.1.7.3 Additional mediation analysis

We additionally investigated whether the effect of early LS on depressive symptoms in young adulthood is mediated by CT alterations in adulthood. There was a negative indirect effect of early LS on depressive symptoms in adults through OFC thickness (indirect effect = .0369, SE = .18, 95 % CI = 0.0081 to 0.0779), with a significant path between early LS and OFC thickness ($\beta = -.209$, SE = .073, $p = .005$) and between OFC thickness and depression scores ($\beta = .185$, SE = .074, $p = .019$). The direct path between early LS and depression scores remained significant ($\beta = .185$, SE = .074, $p = .014$), suggesting that the impact of early LS on depressive symptoms was partially mediated by OFC thickness in young adults.

2.2 Study 2: Coping under stress: Prefrontal control predicts stress burden during the COVID-19 crisis

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2.2.1 Abstract

Background: The coronavirus (COVID-19) pandemic has confronted millions of people around the world with an unprecedented stressor, affecting physical and mental health. Accumulating evidence suggests that emotional and cognitive self-regulation is particularly needed to effectively cope with stress. Therefore, we investigated the predictive value of affective and inhibitory prefrontal control for stress burden during the COVID-19 crisis.

Method: Physical and mental health burden were assessed using an online survey, which was administered to 104 participants of an ongoing German at-risk birth cohort during the first COVID-19 wave in April 2020. Two follow-ups were carried out during the pandemic, one capturing the relaxation during summer and the other capturing the beginning of the second wave of the crisis. Prefrontal activity during emotion regulation and inhibitory control were assessed prior to the COVID-19 crisis.

Results: Increased inferior frontal gyrus activity during emotion regulation predicted lower stress burden at the beginning of the first and the second wave of the crisis. In contrast, inferior and medial frontal gyrus activity during inhibitory control predicted effective coping only during the summer when infection rates decreased but stress burden remained unchanged. These findings remained when controlling for sociodemographic and clinical confounders such as stressful life events prior to the crisis or current psychopathology.

Conclusions: We demonstrate that differential stress-buffering effects are predicted by the neural underpinnings of emotion regulation and cognitive regulation at different stages during the pandemic. These findings may inform future prevention strategies to foster stress coping in unforeseen situations.

2.2.2 Introduction

The coronavirus (COVID-19) pandemic is related to physical health impairments and dramatic changes to everyday life for hundreds of millions of people around the world. With the social contact restrictions beginning in March 2020 in Germany, nearly all schools were closed overnight, working environments changed radically, and social life was restricted probably as never before. Early studies investigating the impact of these initial "first-level threats" (imminent threat) on mental health burden reported elevated levels of perceived stress, anxiety, and depressive symptoms during the first wave of the COVID-19 pandemic (Benke et al., 2020a, 2020b). While sustained socio-economic "second-level threats" continued throughout the time when infection rates lowered during the summer, renewed first-level health threats emerged at the beginning of the second wave of the pandemic in late 2020.

Appropriate coping in response to these time-dependent challenges in the face of an ongoing crisis like the COVID-19 pandemic requires the balanced use of emotional regulation and cognitive control strategies (Feder et al., 2019). While affective control, such as reappraisal, involves the modulation of emotions in response to unpleasant stimuli (Gross, 2015; Holley et al., 2017), cognitive control includes the inhibition of inappropriate or ineffective behavior (Aron, 2007). Both are part of the executive function system and reflected mainly in the prefrontal cortex (PFC) (Davidson et al., 2000; Ochsner et al., 2002). Affective control strategies are associated with an increased activity in the inferior frontal gyrus (IFG), the ventrolateral PFC, dorsolateral PFC, and medial PFC (Gross, 2015; Kanske et al., 2011; Ochsner et al., 2002). Cognitive inhibitory control is linked to activity in the fronto-basal-ganglia circuit including the middle frontal gyrus (MFG), the IFG, and the basal ganglia (Aron, 2007; Aron et al., 2003; Aron et al., 2004; Verbruggen & Logan, 2008), indicating shared neuronal underpinnings within the IFG and MFG.

The present longitudinal study investigates the predictive value of prefrontal activity during an emotion regulation and an inhibitory control task assessed prior to the COVID-19 pandemic for stress burden during the COVID-19 crisis in 104 participants of an ongoing at-risk cohort study following participants since birth. Approximately four weeks after the initial lockdown in Germany in March 2020, participants rated their current stress burden in an online survey (baseline during the first wave). Six to eight weeks later (first follow-up) as well as six months later (at the beginning of the second wave of the pandemic; second follow-up), participants completed the same questionnaire. We expected that higher affective and cognitive control would predict lower stress burden during the COVID-19 pandemic. Moreover, we hypothesized that the ability to control emotions in order to overcome perceived stress burden would be more necessary at the beginning of the first and second wave of the COVID-19 crisis when participants were confronted with direct threat due to high infection and death numbers (first-level threat). By contrast, we expected that cognitive control would become increasingly important in order to cope with the ongoing socio-economic uncertainties during the pandemic (second-level threat).

2.2.3 Materials and methods

2.2.3.1 Sample

The present investigation was conducted within the Mannheim Study of Children at Risk, an ongoing longitudinal study of the long-term outcomes of early psychosocial and biological risk factors following participants since birth (Laucht et al., 2000). The initial sample consisted of 384 children born between 1986 and 1988 in the Rhine-Neckar region of Germany. Infants were recruited from two obstetric and six children's hospitals and were included according to a two-factorial design intended to enrich and control the risk status of the sample (distribution in the current sample: 37 (35.6 %) participants without psychosocial

risk, 35 (33.7 %) with low psychosocial risk, and 32 (30.8 %) with high psychosocial risk at birth).

Up to the time of the lockdown on March 23rd 2020, 165 participants completed an ongoing assessment, including a comprehensive questionnaire package on physical and mental health, a structured clinical interview (SCID-5-CV German version; Beesdo-Baum et al., 2019), and a magnetic resonance imaging (MRI) session, including an emotion regulation and stop-signal task (see below). In April 2020 (during the first wave), two months later (first follow up during summer), and six months later (second follow-up in December), participants were invited to take part in an online COVID-19 questionnaire, adapted and modified from the Coronavirus Health and Impact Survey (CRISIS; Nikolaidis et al., 2020). 133 (80.61 %) participants completed the COVID-19 baseline assessment, of whom 128 (96.24 %) also responded to the first follow-up questionnaire and 116 (87.21 %) to the second follow-up questionnaire. Functional MRI data were available for 104 participants for the baseline and first follow-up questionnaire, and for 95 participants for the second follow-up questionnaire. The study was approved by the Ethics Committee of the University Heidelberg, Germany, written informed consent from all participants was obtained, and participants were financially compensated.

2.2.3.2 Stress burden during COVID-19

To assess the impact and threat of COVID-19 on physical and mental health, we used four items rated on a 10-point Likert scale (0: completely disagree; 10: completely agree). We calculated a sum score for each assessment (baseline, first follow-up, second follow-up).

2.2.3.3 Emotion regulation

Prior to the COVID-19 pandemic, participants performed an adapted and modified version of an emotion regulation task (Hermann et al., 2017) during functional MRI. In brief,

participants were asked to either watch aversive ('$Look_{negative}$') or neutral ('$Look_{neutral}$') pictures from the International Affective Picture System (IAPS; Lang et al., 1999) or to reappraise negative pictures ('Reappraisal'). In the reappraisal condition, participants were asked to use the strategy of reappraisal to decrease the intensity of their negative affect. The participants were carefully instructed to either view the depicted scenario from a more positive or at least a less negative point of view (e.g., a person in jail might be a famous actor) or to rationalize the presented picture (e.g., due to enormous advances in modern medicine, a very premature baby may have an entirely normal life). During the neutral conditions, participants were instructed to simply watch the depicted scenarios without actively changing their emotional state evoked by the pictures.

The task consisted of a randomized block design, in which every block started with a jittered 3 s presentation of the instruction form (i.e., 'Look' or 'Reappraise'). Subsequently, participants viewed either four negative or four neutral pictures for 5 s each according to the presented condition, and were asked to rate the intensity of currently perceived negative feelings on a 7-point Likert scale (1 = no negative feelings at all; 7 = extremely negative feelings) via a button press (max. 4 s). Subsequently, a white fixation cross on black background was presented during the inter-trial-interval up to a total block duration of 30 s. The total task comprised four blocks per condition (12 blocks in total) and lasted for 6 min 37 s. The blocks were arranged in four runs with a randomized presentation of all conditions within each run, leading to a maximum of two presentations of the same condition in succession.

2.2.3.4 Inhibitory control

Participants completed the stop-signal task (SST) to assess cognitive inhibitory control during functional MRI (Rubia et al., 2003). Each trial began with a fixation cross (500 ms), which was followed by an arrow pointing to the left or right (go-signal). In the go-trials (75 %

of a total number of 160 trials), participants were instructed to react to the arrow as quickly and accurately as possible by pressing either the left or the right button according to the previously shown arrow. Stop-trials (25 % of a total number of 160 trials) were designed as trials in which a go-signal was followed by an arrow pointing upwards (stop-signal). During the stop trials, participants were instructed to inhibit their response (yielding successful vs. unsuccessful inhibition). The delay between a go-signal and a stop-signal (stop-signal delay; SSD) started at 250 ms and was dynamically changed according to the participant's performance using an adaptive algorithm. The SSD latency increased by 50 ms whenever the participant correctly inhibited the previous response (max. 900 ms), making it more difficult to stop. In contrast, the SSD latency decreased by 50 ms whenever the previous stop-trial was incorrectly answered (min. 50 ms). Using this procedure, an approximately equal number of successful and unsuccessful stop-trials can be achieved. Moreover, we excluded participants with a negative stop-signal reaction time (SSRT). Prior to scanning, all participants were given clear instructions. Total scanning time was 6 min 37 s.

2.2.3.5 Functional MRI data acquisition and preprocessing

Functional MRI data collection consisted of a localizer scan followed by a blood oxygen level-dependent (BOLD)-sensitive T2*-weighted echo-planar imaging (EPI) sequence and structural T1-weighted sequence using a 3T-scanner (PrismaFit; Siemens) with a standard 32-channel head coil. For functional imaging, a total of 186 volumes with 36 slices covering the whole brain (matrix 64 x 64, resolution 3.0 x 3.0 x 3.0 mm with 1 mm gap, repetition time = 2100 ms, echo time = 35 ms, flip angle = 90°) were acquired for each task. The slices were inclined 20° from the anterior/posterior commissure level. The first 11 volumes of the emotion regulation task and the first six volumes of the SST were discarded to allow longitudinal magnetization to reach equilibrium.

2.2.3.6 Functional MRI data analyses and statistical analyses

Statistical parametric mapping version 12 (SPM12) implemented in MATLAB R2017b was used to analyze functional MRI data. Preprocessing included slice time correction of the volumes to the first slice, realignment to correct for movement artifacts, co-registration of functional and anatomical data, spatial normalization to standard Montreal Neurological Institute (MNI) space, and spatial smoothing with a Gaussian filter of 8 mm full-width at half maximum.

For the emotion regulation task, individual first-level contrasts based on onsets and durations of each condition were convolved with the canonical hemodynamic response function (HRF) in order to model the BOLD time course by using general linear models. Six motion parameters were included as regressors of no interest. For the group-level analysis, individual contrast images of the Reappraisal > $Look_{neutral}$ condition were entered into a random-effects analysis to assess emotion regulation.

Similarly, for the SST, individual first-level contrasts for the onsets of the four event types (correct go-trials, incorrect go-trials, successful inhibition, and unsuccessful inhibition) were modeled using delta functions convolved with the canonical HRF. Again, six motion estimation parameters were included as regressors of no interest. Second-level random effects analyses were modeled for the contrast of interest, i.e., successful inhibition was determined by contrasting successful stop-trials with unsuccessful inhibition and correct go-trials [successful inhibition > (unsuccessful inhibition - correct go-trials)]. Whole-brain differences in activation for the contrasts of interest for both tasks were estimated using t-tests at a family-wise error (FWE) corrected p-value of .05.

The IFG and the MFG were defined as regions of interest (ROIs) based on previous studies reporting a strong involvement in emotion regulation and inhibitory control, and their potential relevance in natural disasters (Boccia et al., 2016; Gavazzi et al., 2020; Grecucci,

Giorgetta, Bonini, et al., 2013; Grecucci, Giorgetta, Van't Wout, et al., 2013). To extract predefined ROIs, anatomical masks implemented in the Wake Forest University (WFU) PickAtlas v2.4 (Maldjian et al., 2003) were used, where a $p < 0.05$ FWE correction (minimum of 10 adjacent voxels) was applied. Mean contrast values of each participant were extracted from the FWE-corrected significant clusters in the contrasts of interest (Table 3) and exported to SPSS Statistics 25. The predictive power of IFG and MFG activity during affective and inhibitory control for the impact of COVID-19 on mental and physical health was investigated using linear regression models controlling for all covariates (see below). Moreover, a conservative Bonferroni correction was applied for the hemispheres, two regions of interest (MFG and IFG), and for affective and cognitive control (α of 0.05 divided by 8 tests, resulting in $\alpha_{adj} = .0063$). Additional sensitivity analyses were performed to control for the robustness of significant effects.

Table 3. Results of the regions of interest analyses for the emotion regulation task and the stop-signal task

ROI					MNI Coordinates		
		k	$P_{FWE-corr}$	T	X	Y	Z
Emotion Regulation Task							
Left	IFG	509	<.001	10.46	-36	26	-1
Right	IFG	338	<.001	9.91	51	26	-1
Left	MFG	406	<.001	10.54	-42	2	53
Right	MFG	174	<.001	8.03	51	11	44
Stop-Signal Task							
Left	IFG	50	.001	4.76	-48	41	8
Right	IFG	34	<.001	5.23	51	38	14
Left	MFG	200	<.001	7.57	-27	29	50
Right	MFG	200	<.001	7.48	30	20	50

Note: FWE-corr = family-wise error corrected; IFG = Inferior frontal gyrus; k = Cluster size; MFG = Medial frontal gyrus; MNI = Montreal Neurological Institute

2.2.3.7 Covariates

Several important covariates were added to the main analyses, including gender, psychosocial adversity and obstetric risk at birth, current diagnoses of a mental disorder (assessed prior to the pandemic), as well as current life events prior to and during the COVID-19 pandemic.

2.2.3.8 Psychosocial adversity

Psychosocial adversity was assessed using a standardized parent interview according to an enriched family adversity index (Rutter & Quinton, 1977) at the participants' age of 3 months. The interview comprised 11 items covering characteristics of the family environment, the parents, and the parents' partnership (e.g., presence of parental psychiatric disorders, overcrowding in the home, ongoing parental conflicts, or unwanted pregnancy) during a period of one year prior to the assessment. A sum score of psychosocial adversities was calculated by adding up the presence of all items.

2.2.3.9 Obstetric risk at birth

Obstetric adversity was assessed using a standardized parent interview conducted at the participants' age of 3 months. A sum score of obstetric risk factors was computed by adding up the presence of nine adverse conditions during pregnancy, delivery, and in the early postnatal phase, such as preterm birth or low birth weight (Laucht et al., 2000).

2.2.3.10 Life events

Life events were recorded using a modified version of the Munich Events List (MEL; Maier-Diewald, 1983) within the online questionnaire at all three time points. The MEL covers several areas of acute and chronic, positive and negative stressors, including marriage, delivery of a child, but also negative health outcomes, illness of a relative or job loss. We

adjusted the items depending on the time point, i.e., presence of life events between the regular assessment wave and prior to the COVID-19 crisis for the COVID-19 baseline assessment, and life events between baseline assessment and first follow-up as well as between the first and second follow-up for both COVID-19 follow-up assessments, respectively.

2.2.3.11 Sensitivity analyses

Further sensitivity analyses were calculated to control for the robustness of the predictive value of the neural activity, including parenthood, household income, current work status, workplace changes, and whether the participants were critical workers for the COVID-19 response as additional covariates.

2.2.4 Results

2.2.4.1 Descriptive data and changes of COVID-19 impact

Descriptive data are depicted in Table 4. There were significant differences for the reported physical and mental impact of the COVID-19 pandemic between the baseline assessment and the follow-up assessments ($F = 11.812$, $p < .001$). Post-hoc analyses revealed no significant differences between the baseline assessment and the first follow-up ($p = .894$), but significant differences emerged between the baseline and the second follow-up ($T = -4.306$, $p < .001$), and between the first and second follow-up ($T = -3.912$, $p < .001$), suggesting a continuous burden on mental and physical health since the beginning of the COVID-19 outbreak, with a further increased stress burden at the beginning of the second wave of the pandemic.

Table 4. Sample description and descriptive data

Total n = 104			
	N	*%*	
Sex (female)	58	55.8	
Critical worker status	39	37.5	
Full-time employment	*64*	*61.5*	
Workplace changes due to COVID-19	*69*	*66.3*	
Parenthood	45	43.3	
Current mental disorder	*28*	*26.9*	
	Mean	*SD*	*range*
Age	33.31	0.54	32.25 - 34.25
COVID-19 impact (baseline)	12.13	5.92	4 - 25
COVID-19 impact (1st follow-up)	12.22	6.09	4 - 27
COVID-19 impact (2nd follow-up)[A]	14.39	5.68	4 - 26
Psychosocial risk factors at birth	1.80	1.90	0 - 7
Obstetric risk factors at birth	0.83	0.90	0 - 4
Income (in €)	4110	1816	450 - 8789
Life events prior to COVID-19[B]	4.41	4.79	0 - 26
Life events during COVID-19[B] (1st follow-up)	1.37	1.86	0 - 7
Life events during COVID-19[A,B] (2nd follow-up)	1.76	1.75	0 - 8

Note: A. Sample size comprises participants who took part in the fMRI assessments and all follow-up questionnaires (n = 95). B. Higher scores of life events prior to COVID-19 resulted from retrospective assessment of a longer time period (i.e., time between regular assessment wave and baseline COVID-19 assessment) compared to life events during COVID-19 (time between baseline COVID-19 assessment and follow-up assessments).

2.2.4.2 COVID-19-related stress burden at the baseline assessment

Higher right IFG activity during the emotion regulation task was associated with a lower stress burden at the baseline assessment (β = -.281, T = -3.023, p = .003, Figure 5a), after controlling for gender and psychosocial and obstetric risk factors at birth, current mental disorder prior to the COVID-19 pandemic, and current life events. In contrast, left IFG and bilateral MFG activity during emotion regulation were not related to stress burden at the beginning of the COVID-19 crisis (p > .121). In addition, inhibition-related right MFG activity was negatively associated with the COVID-19 burden at the baseline assessment (β = -.215, T = -2.220, p = .029), although this was not significant after correction for multiple testing. No significant relationships emerged with regard to left MFG and IFG (all Ps > .07) activity during inhibition.

2.2.4.3 COVID-19-related stress burden at the first follow-up assessment

During the first follow-up assessment in the summer, neither IFG nor MFG during emotion regulation was related to the COVID-19 impact (all Ps > 0.61), suggesting that affective control did not predict stress burden at this point of time. In contrast, lower right IFG and right MFG activity during inhibitory control was associated with a higher COVID-19 stress burden at the first follow-up assessment, even when controlling for the above-mentioned covariates (right IFG: β = -.348, T = -3.638, p < .001; right MFG: β =- .375, T = -3.884, p < .001, Figure 5b&5c). Moreover, a negative association for left MFG activity emerged, which did not survive correction for multiple comparisons after including the above-mentioned covariates (β = -.250, T = -2.582, p = .011). Inhibition-related left IFG activity was not related to stress burden at the first follow-up (p = .093).

2.2.4.4 COVID-19-related stress burden at the second follow-up assessment

Higher right IFG activity during the emotion regulation task was associated with a lower stress burden at the second follow-up assessment (β = -.327, T = -3.246, p = .002, Figure 1d), after controlling for the above-mentioned covariates. In contrast, left IFG and MFG activity during emotion regulation were not related to stress burden during the second wave of the COVID-19 pandemic (all Ps > .086). Likewise, inhibition-related activity was not related to COVID-19 burden at the second follow-up (all Ps > .105).

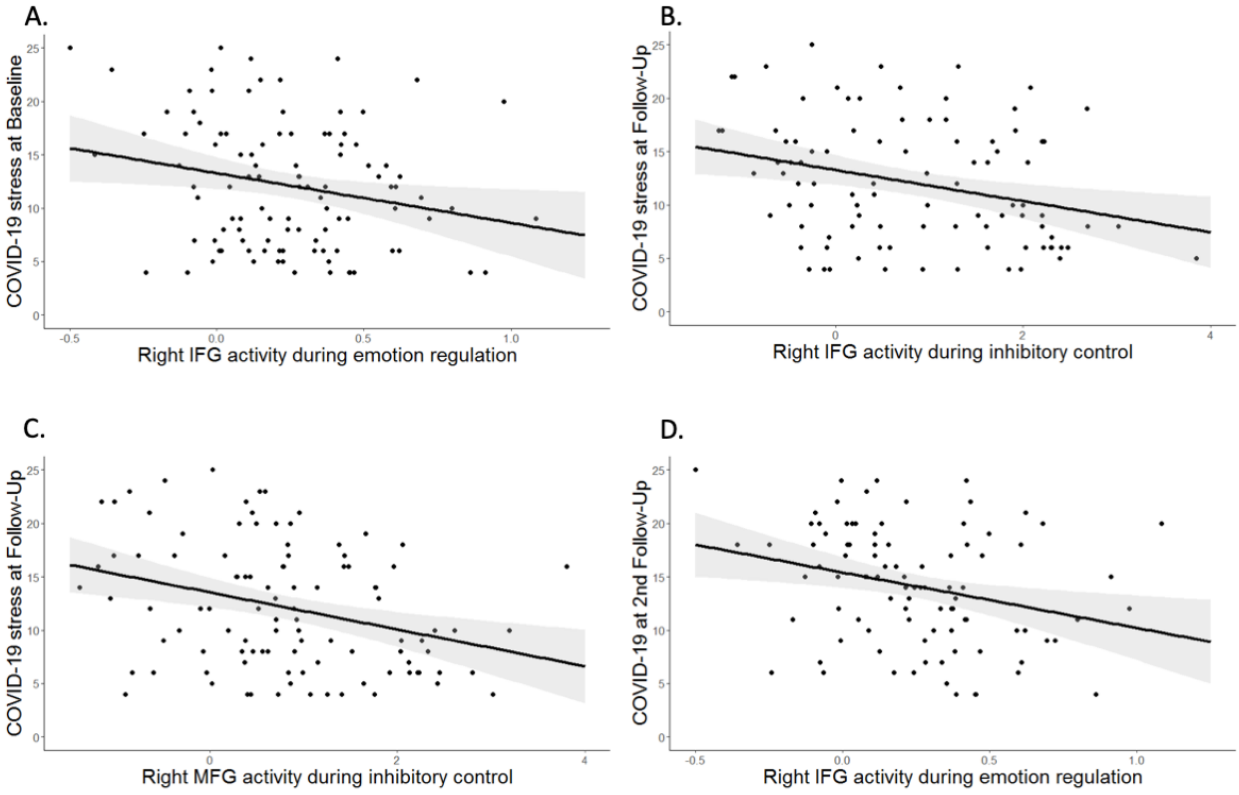

Figure 5. (A) Association of right IFG activity and COVID-19 impairments at the baseline assessment. Higher affective control was related to decreased stress burden during the first wave of the COVID-19 pandemic. (B) and (C) Association of right IFG activity and right MFG activity and COVID-19 impairments at the first follow-up assessment during the summer. Higher cognitive activity was related to decreased stress burden caused by the COVID-19 pandemic. (D) Association of right IFG activity and COVID-19 impairments at the second follow-up assessment. Higher affective control was related to decreased stress burden at the beginning of the second wave of the pandemic.

Table 5. Results of further sensitivity analyses using brain activity as main predictor to explain stress burden.

Covariate	ROI	Task / Assessment	Beta	*T*	p-value
Parenthood	Right IFG	Emotion Regulation / Baseline	-.259	-2.681	**.009**
	Right MFG	Stop-Signal Task / Follow-Up	-.333	-3.428	**.001**
	Right IFG	Stop-Signal Task / Follow-Up	-.313	-3.288	**.001**
	Right IFG	Emotion Regulation / 2nd Follow-Up	-.325	-3.203	**.002**
Income	Right IFG	Emotion Regulation / Baseline	-.288	-2.997	**.003**
	Right MFG	Stop-Signal Task / Follow-Up	-.351	-3.574	**.001**
	Right IFG	Stop-Signal Task / Follow-Up	-.294	-2.973	**.004**
	Right IFG	Emotion Regulation / 2nd Follow-Up	-.339	-3.404	**.001**
Current work status	Right IFG	Emotion Regulation / Baseline	-.275	-2.853	**.005**
	Right MFG	Stop-Signal Task / Follow-Up	-.375	-3.866	**< .001**
	Right IFG	Stop-Signal Task / Follow-Up	-.319	-3.268	**.001**
	Right IFG	Emotion Regulation / 2nd Follow-Up	-.311	-3.182	**.002**
Critical worker status	Right IFG	Emotion Regulation / Baseline	-.271	-2.858	**.005**
	Right MFG	Stop-Signal Task / Follow-Up	-.367	-3.765	**< .001**
	Right IFG	Stop-Signal Task / Follow-Up	-.306	-3.113	**.002**
	Right IFG	Emotion Regulation / 2nd Follow-Up	-.324	-3.221	**.002**
Workplace changes	Right IFG	Emotion Regulation / Baseline	-.271	2.803	**.006**
	Right MFG	Stop-Signal Task / Follow-Up	-.363	-3.702	**< .001**
	Right IFG	Stop-Signal Task / Follow-Up	-.311	-3.148	**.002**
	Right IFG	Emotion Regulation / 2nd Follow-Up	-.323	-3.225	**.002**

2.2.4.5 Sensitivity analyses

Separate subsequent sensitivity analyses were calculated including additional control variables such as parenthood, income, current work status, critical worker status, and

workplace changes due to the COVID-19 pandemic. None of the sensitivity analyses changed the results (Table 5).

2.2.5 Discussion

To the best of our knowledge, this is the first study to report a differential predictive value of emotion- and inhibition-related prefrontal control for stress burden at the beginning of and during the COVID-19 crisis (Figure 6).

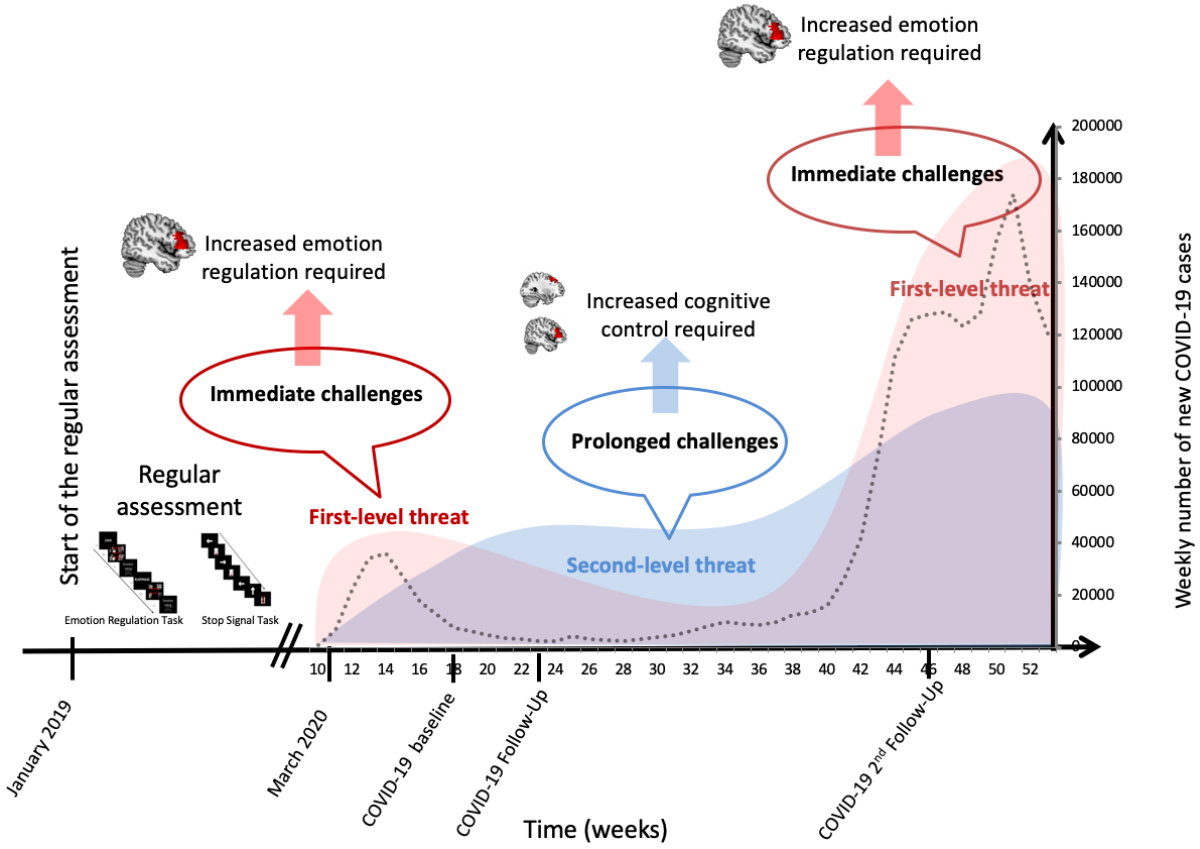

Figure 6. Timeline and proposed stress model at different stages during the COVID-19 pandemic. An initial high load of emotional distress requires adequate affective coping of the IFG at the beginning of the first and the second wave of the COVID-19 pandemic. Prolonged socio-economic uncertainties involve cognitive control of the IFG and MFG to overcome these challenges during the ongoing crisis.

Note: Weekly statistics on COVID-19 cases are freely available from the Robert Koch Institute, Berlin, Germany.

Specifically, we found a significant negative relationship between right IFG activity during emotion regulation assessed prior to the COVID-19 pandemic and stress burden approximately four weeks after the lockdown in Germany. In light of unforeseen first-level threat entailing immediate danger to health and emotional challenges due to the dramatic, unprecedented social contact restrictions at the beginning of the crisis with high levels of emotional arousal, fear, and the imminent feeling of loneliness (Bauerle et al., 2020; Brooks et al., 2020; Dubey et al., 2020; Odriozola-Gonzalez et al., 2020), affective coping was particularly needed (Groarke et al., 2020; Restubog et al., 2020). Our results support this assumption, indicating that participants who are characterized by higher affective control were able to cope better with these initial threats and uncertainties of an unprecedented stressor like the COVID-19 pandemic. At the first follow-up assessment, which occurred during the summer when the first-level threat decreased due to loosened restrictions and lower infection rates. Also, emotional habituation may occur if participants are confronted with the same stressor for a longer amount of time (Grissom & Bhatnagar, 2009). These reasons both may contribute to a decreased necessity for affective coping. Notably, towards the second wave of the pandemic, when infection rates increased dramatically even above those during the first wave and a second lockdown was imposed, affective coping was again required to face this immediate, even more intense, threat.

In contrast, we found an increased need for cognitive control strategies when facing second-level threat, i.e., socio-economic uncertainties. Specifically, higher cognitive inhibition-related activity in the right MFG and IFG predicted lower COVID-19 distress only at the first follow-up (when restrictions had eased), but was unrelated to stress burden at the beginning of the first wave (baseline) and the second wave (second follow-up). While there was an immediate threat at the beginning of both the first and the second wave, the progression of the pandemic is characterized by ongoing socio-economic challenges, uncertainties about one’s own future financial and work capabilities, reduced working hours,

and the length of the crisis (Cutler & Summers, 2020; Fegert et al., 2020). These sustained and secondary challenges (Pedrosa et al., 2020) require increased cognitive coping and flexibility over time, thus explaining the negative association of the MFG and IFG activity with stress burden at the first follow-up.

Given the unique prospective design of our study, we were able to demonstrate the strong predictive value of neural activity for stress coping during the pandemic, irrespective of the presence of several important factors which have previously been reported to affect stress coping. Specifically, the findings were robust against control for the presence of other current stressful life events (Undheim & Sund, 2017), socio-economic disadvantages (McEwen & Gianaros, 2010), the occurrence of early life psychosocial adversities (Quinlan et al., 2017; Sheffler et al., 2019), or the presence of a mental disorder before the crisis (Joormann & Gotlib, 2010), thus highlighting the superior role of neural self-regulation for coping under stress.

Our results provide a substantial contribution to the existing literature, and have important implications not only for affective and cognitive coping with potential further waves of increasing COVID-19 cases, for instance due to virus mutations around the world, but also with unprecedented stressful events in general. Specifically, we argue that there is a particular need for prevention strategies which aim at improving the individual's affective and cognitive coping capacities in response to unforeseen events with a high stress load. As such, we suggest that stepped care neuromodulation might mitigate stress burden via gaining self-control over neural affective and cognitive regulation. Therefore, enhancing neuroplasticity through different methods, such as mindfulness or even neurofeedback in emotion regulation areas might offer the potential to acquire and foster primary preventive self-regulation skills when initially encountering stressful events, whereas learning self-control over cognitive regulation activity might rather serve as a secondary prevention tool during ongoing stressful events. In addition, ecological momentary assessment (EMA) might be a promising,

affordable tool to further foster affective and cognitive control strategies in response to real-time, real-life stressors on an individual's own smartphone; this could be addressed by future intervention studies.

Some limitations of our findings need to be addressed. Only a third of our initial sample was able to take part in all COVID-19 assessments. Moreover, despite the quick start, we were unable to include the first days of the lockdown, which might have exerted the greatest effects on perceived stress. However, since we were particularly interested in coping with stress burden caused by the crisis, this time period appears to be appropriate to capture stress burden given that previous studies found no differences when comparing well-being, anxiety and depression in the initial phase of the pandemic to four weeks later (Vindegaard & Benros, 2020).

In the framework of an ongoing longitudinal study following at-risk participants since birth, we thus provide first evidence for the predictive value of neural underpinnings of emotion regulation during the first and second lockdown and cognitive regulation during the COVID-19 pandemic between both waves. These findings may inform future prevention strategies seeking to foster stress coping in unforeseen situations.

3 GENERAL DISCUSSION

This thesis aimed at (1) investigating the long-term consequences of life stress experienced at different developmental stages from infancy to adolescence on prefrontal brain morphology, and (2) evaluating the predictive value of neural activity assessed during an emotion regulation task and inhibition control paradigm on coping with perceived physical and mental stress facing the acute stressor of a global health crisis. Given the unique longitudinal data available in the framework of the Mannheim Study of Children at Risk, the main findings of this thesis were that (1) early life stress that occurred in infancy was linked to CT reductions in the OFC in adulthood. Critically, life stress during childhood and adolescence was not related to CT alterations in adults. Moreover, the relationship between early life stress and orbitofrontal CT was partially mediated by depressive symptoms during late adolescence and young adulthood. (2) Increased neural activity in prefrontal regions assessed in an emotion regulation task and a stop-signal task predicted less self-reported burden during the COVID-19 pandemic, an unprecedented natural catastrophe. Remarkably, while adequate emotion regulation was particularly needed at the beginning of the crisis and during the second wave, when imminent health threats due to heightened infection rates were present, effective inhibitory control was required during the course of the pandemic, when confronted with ongoing uncertainties.

Early life adversity is highly prevalent in psychiatric disorders with findings ranging from 18 to 58 % of psychiatric patients reporting at least one major life event in early years (Benarous et al., 2017; Pietrek et al., 2013; Riedl et al., 2020). Besides its high prevalence in clinical samples, the consequences of early life adversities have been extensively investigated. Several studies reported the detrimental impact of early life adversities on mental health

(Scott et al., 2010), but also on physical health, with findings also indicating poorer socio-economic success in later life and decreased life expectancy associated with early life stress (Anda et al., 2006; Felitti et al., 1998; Hardcastle et al., 2018). Increasing evidence highlights the relevance of timing, type and chronicity of adverse events, with several studies pointing to highly sensitive periods ranging from infancy to adolescence during which an individual is particularly vulnerable to environmental stress (Lupien et al., 2009).

Notably, mounting evidence also points to stress-sensitive periods in the developing brain. In particular, the PFC is considered as a region with ongoing postnatal growth and maturation, reaching its peak volume not before adolescence (Andersen & Teicher, 2008; Gee & Casey, 2015; Lenroot & Giedd, 2006). Therefore, a variety of studies focused on alterations in the PFC related to early life adversities, with findings predominantly reporting volume reductions in this region (for instance Hanson et al., 2010; Holz et al., 2015). However, most of the studies relied on retrospectively collected data, which are highly prone to recall-bias (Coughlin, 1990). Besides that, and just as important, it is highly difficult to determine the exact time point of early life stress using retrospective assessments, especially when asking adults about perceived stress, for instance during infancy (Alberini & Travaglia, 2017). Study 1, therefore, fills an important gap in the literature using carefully collected longitudinal data of an at-risk cohort study following its participants since birth. Given this approach, we were able to determine life stress occurring from infancy to adulthood prospectively and accurately without relying on retrospectively collected data. Moreover, the study design enabled us to control for important confounding factors, such as early substance abuse or a lifetime diagnosis of an affective or anxiety disorder.

In line with previous findings our results highlight infancy as a crucial period during which the PFC, particularly its orbitofrontal part, is highly sensitive to environmental stress (study 1). While previous studies mainly focused on cortical volume alterations (Hanson et al., 2010; Holz et al., 2015), we expand those finding towards CT alterations. Indeed, gray

matter volume is a composite measure consisting of CT and surface area, which follow distinct maturational trajectories given their differential genetic determination (Panizzon et al., 2009; Raznahan et al., 2011). Therefore, studies investigating these distinct neural markers are particularly warranted. CT is considered to rapidly increase in infancy, before an abrupt decrease begins in adolescence and young adulthood followed by a steady decline thereafter (Ducharme et al., 2016; Forde et al., 2017; Frangou et al., 2021; Lyall et al., 2015; Petanjek et al., 2011). Reductions in CT in young adulthood therefore can either be explained by an initial delay in early maturation given the impact of early life stress or might reflect premature cortical thinning. Normal perinatal brain development is characterized by an increased synaptic growth, resulting in an overproduction of synaptic interconnections in the PFC and other regions (Forde et al., 2017; Petanjek et al., 2011). Early life stress, however, might disrupt this normal development of synaptic proliferation, resulting in altered synaptic pruning. On the short run, this process might lead to an initial adequate adaptation to the given environment, but, in turn, might represent a long-term detrimental alteration, lasting until adulthood. The latter, however, can be caused by ongoing environmental adversities throughout the life span, reflecting for instance a noxious lifestyle, educationally alienated environments, or socioeconomic disadvantages, which have been consistently shown to be common following early life stress (Garner, 2013; Shonkoff et al., 2009; Shonkoff et al., 2012). This ongoing toxic stress might act as acceleration in maturational processes and in turn lead to accelerated cortical thinning in adults exposed to environmental adversities. To clarify and disentangle the pathways proposed above longitudinal MRI studies assessing cortical development prospectively from infancy to adulthood in the same individuals are thus particularly needed.

Besides its impact on brain alterations, ELS is highly linked to mood- and stress-related disorders, such as MDD (Nelson et al., 2017). Experiences of adverse events are further associated with an increased risk of an early onset, increased persistence, and

diminished treatment-reactivity in MDD (Nelson et al., 2017). Given these results, study 1 expands the existing literature by introducing a mediation model explaining the relationship of ELS, MDD symptoms, and CT alterations. Specifically, our study first replicated findings of previous studies documenting a strong relationship between ELS and MDD symptoms. Additionally, we were able to demonstrate the mediating role of MDD symptoms in adolescence on the association of ELS and CT in adults. That is, increased exposure to ELS was associated with elevated levels of depressive symptoms during adolescence which, in turn, predicted reduced CT in adulthood. The mediation model finally showed that the link between ELS and CT reductions in adulthood was partially explained by MDD symptoms in late adolescence and early adulthood. Therefore, our model suggests that increased levels of ELS may foster the risk for an anhedonic lifestyle, which is marked by a diminished experience of pleasure, reduced social and physical activities, and heightened physiological arousal. This precursor of depressive symptoms may, in turn, increase the risk for ongoing neurotoxic effects affecting the typical neural development.

However, given the temporal order of our assessments, we cannot rule out the possibility of an inverse effect. More specifically, CT alterations in the OFC may, in turn, act as a mediator of the impact of ELS on MDD symptoms in adulthood. Indeed, a study by Foland-Ross found that CT reductions in the OFC predicted the onset of depression symptoms in a sample of adolescent girls followed prospectively (Foland-Ross et al., 2015). These findings thereby suggest CT alterations as a potential risk factor for psychopathology. Importantly, future studies are needed to address these differential pathways by analyzing longitudinal MRI studies with regard to ELS and psychopathology.

Given the outlined imminent and sustained impact of adverse events on an individual's mental and physical constitution, the critical question arises why some people suffer from these adversities while others seem to withstand those challenges unhurt. Coping with and under stress has become a growing research field of interest, often referring to the

concept of resilience (Feder et al., 2019; Feder et al., 2009). In psychological and medical research, the term resilience was first established after a longitudinal study following children living in Hawaii under tenuous and risky conditions which surprisingly found that a majority of those children developed mentally unscathed (Werner, 1993). Broadly defined, resilience means maintaining mentally healthy despite the exposure to stressful events, chronic adversities or traumatic experiences (Fletcher & Sarkar, 2013). Thereby, resilient individuals are considered to be characterized by higher trait optimism, heightened levels of self-esteem, and increased social support (Collins, 2007; Gupta & Bonanno, 2010; Herrman et al., 2011; Tugade & Fredrickson, 2004). Moreover, resilience is considered as a collection of adaptive behavioral and cognitive abilities, including adequate emotion regulation, inhibitory control, or cognitive flexibility (Campbell-Sills et al., 2006; Feder et al., 2019). Indeed, a variety of studies investigated the beneficial impact of adequate coping in the light of resilience and adverse events (Caston & Mauss, 2011; Gloria & Steinhardt, 2016; Min et al., 2013). However, most of these studies investigated difficulties in emotion regulation or inhibitory control either after a traumatic event or in response to an artificially induced acute stressor (e.g., TSST; Cavanagh et al., 2014; Roos et al., 2017; Shapero et al., 2019). Given these approaches, limited conclusions on future coping with a naturally occurring stressor are possible.

Study 2 addressed this limitation by using functional MRI data assessed prior to the COVID-19 pandemic, a worldwide health hazard having a tremendous impact not only on physical health but also on mental health, to predict coping during this unprecedented crisis. Specifically, we assessed two distinct coping strategies, emotion regulation and inhibitory control, during well-established functional MRI tasks within a regular assessment wave in the framework of a longitudinal study. Shortly after the first lockdown due to the crisis in March 2020, once repeated during the summer, when infection cases were low, and once at the beginning of the second wave of the pandemic in November 2020, participants rated their

perceived stress burden in an online survey. Overall, we found that adequate coping successfully predicted lower stress burden during the course of this pandemic. Specifically, adaptive emotion regulation was particularly needed in response to immediate threats, which occurred especially at the beginning of the first and second wave of the crisis, when infection rates dramatically increased. In contrast, effective inhibitory control predicted lower stress burden in response to sustained threats, i.e., during the summertime, when infection rates decreased but economic challenges and cognitive uncertainties remained.

Taken together, the findings of this thesis highlight the detrimental long-term impact of environmental adversities and demonstrate the importance of effective coping mechanisms, thereby encouraging the need for successful prevention and intervention strategies. Indeed, a variety of earlier studies already demonstrated the efficacy of emotion regulation trainings in healthy and mentally ill individuals. For instance, Denny and Ochsner provided healthy participants with four laboratory sessions of exercise in different strategies of reappraisal, distancing, and reinterpretation (Denny & Ochsner, 2014). Compared to a control group, which did not receive any intervention, both training groups reported reduced negative affect over time. Even more, those trained in distancing experienced less stress in daily life, indicating a successful adaption of laboratory induced reappraisal training into everyday life. In a study with socially anxious participants, Kivity and Huppert investigated the effect of one week of cognitive reappraisal training (Kivity & Huppert, 2016). Participants received text messages every morning to reappraise anxiety-eliciting social situations throughout the day. A control group was instructed to monitor their feelings during social situations. In the evenings all participants were asked to complete different questionnaires on social anxiety, stressful situations, and the use of reappraisal. Interestingly, while daily anxiety levels did not differ between both groups, participants who were trained in reappraisal, reported lower symptom severity and greater self-efficacy in the use of reappraisal in everyday life. Remarkably, behavioral findings on inhibitory control training are less consistent. For example, Enge found

no differences in inhibitory control performance between a training group, which practiced adaptive versions of a stop-signal and a go/no-go task for three weeks, and an active control group, which received non-adaptive versions of the tasks (Enge et al., 2014). In contrast, Berkmann found increased task performance on the SST in participants who received 10 sessions of inhibitory control training compared to those who performed a mock training (Berkman et al., 2013). Interestingly, the authors provide initial evidence for changes in neural activity, particularly in the IFG, when comparing pre-training to post-training functional MRI data.

Following the neural findings in our study, a promising approach in further enhancing and modulating adequate coping mechanisms is represented by neuromodulation methods. For instance, neuro- or biofeedback comprise a variety of techniques in which distinct unconscious psychophysiological signals, for instance skin conductance, heartrate or brain activity, are recorded and simultaneously displayed to a subject. Real-time functional MRI neurofeedback (rt-fMRI-NF) measures the BOLD signals from pre-defined brain areas in real-time and reflect changes immediately to the subject. Based on operant conditioning, an individual is thereby trained to control and to regulate those self-regulation processes (Sherlin et al., 2011). By now, growing evidence supports the success of neurofeedback in regulation and learning of brain- and body-related activity in both healthy adults, but also in clinical samples with the long-lasting effects to remain unclear (Aggensteiner et al., 2019; Mehler et al., 2018; Young et al., 2014). Moreover, several studies investigated neurofeedback training in emotion regulation, using a variety of methodological approaches, including different target brain areas and different target populations (Linhartova et al., 2019). However, while the results demonstrate promising effects for several brain areas (i.e., amygdala, anterior insula, OFC), and different psychiatric disorders (i.e., MDD, PTSD, anxiety disorders, ADHD) the transferability to and the access in everyday life seems, at least for the moment, visionary, given the enormous technical and financial requirements.

In contrast, mobile health assessments and interventions, such as ecological momentary assessments (EMA) or interventions (EMI), might act as promising and yet affordable approaches to foster coping mechanisms in real-time and real-life. Mobile health instruments are usually based on well-established psychotherapeutic treatments, such as cognitive behavioral therapy (CBT), and often comprise applications which can be used on one's own individual smartphone, tablet or portable computer (Grundahl et al., 2020; Staiger et al., 2020). Using this approach, a lot more individuals seeking help for mental health impairments might be able to receive individualized treatments or training programs in their natural environment (Grundahl et al., 2020). In addition, digital treatments and interventions, such as EMI, offer clinicians and researchers a new objective instrument in managing and following an individual's therapeutic process and progress (Gaggioli & Riva, 2013). A recent review summarized findings of 26 studies applying different parts of previously established CBT elements through EMI (Marciniak et al., 2020). Overall, EMIs had a positive impact on the participants, who reported increased levels of well-being and decreased mental health symptoms (Marciniak et al., 2020), thereby demonstrating the potential benefit from EMI in mental health. Further, during the COVID-19 pandemic, when access to regular therapeutic programs were limited (Taylor et al., 2020), an EMI study conducted over 14 days and targeting self-compassion showed positive effects on perceived stress (Schnepper et al., 2020). However, given the relatively young era of EMIs, studies investigating the long-term efficacy of mobile interventions are sparse but highly needed (Grundahl et al., 2020). While EMIs are especially designed to reach their users in a real-life environment, the controllability of environmental and individual covariates, such as being in company or adjusting your daily routines to the notifications, might be challenging (Vaessen et al., 2019).

An alternative to overcome those limitations might be the usage of virtual reality (VR) applications. VR applications in mental health research are designed to create a virtual but realistic and, importantly, secure world which fulfills the needs for both the users but also the

researchers (Valmaggia, 2017). A major strength of VR is its high ecological validity and its additional controllability for complex environmental confounders (Parsons et al., 2017). Moreover, real-time assessments of physiological, behavioral, and emotional responses during VR are yet applicable and adjustable for distinct populations by combining VR with neurofeedback techniques (Blume et al., 2017; Schoeller et al., 2018; Vourvopoulos et al., 2019), increasing the beneficial usage of VR trainings. A recent review investigating the impact of emotion regulation training on well-being in VR found promising effects in 11 included studies, indicating that VR might help healthy individuals but also patients suffering from mental disorders to alter and improve their emotion regulation abilities in specific virtual environments and situations (Montana et al., 2020). In addition, Manasse used VR to train inhibitory control in participants with binge-eating disorder, which is characterized by a self-perceived loss-of-control in eating behavior (Manasse et al., 2021). The authors administered VR training to 14 participants for two weeks in their natural environment and found a decrease in self-perceived loss-of-control and, importantly, high percentage of acceptability and commitment of the participants. However, further randomized control trials with larger and more heterogeneous samples are necessary to provide additional evidence for the efficacy of VR training related to coping strategies.

3.1 Limitations

Some limitations within the presented studies need to be addressed. Study 1 found that exposure to life stress in infancy predicts CT reductions in the OFC around 25 years later. However, since structural data was only assessed in adulthood, there is no developmental perspective of CT alterations from infancy to adulthood. Therefore, study 1 cannot rule out the possibility that these structural differences were already present in infancy. Nor can study 1 draw a definite conclusion at which time point during development these changes might have occurred in case they were not initially present. Further, study 1 involved only

currently healthy participants at the time of the MRI acquisition, while controlling for lifetime diagnoses of affective or anxiety disorders. Given this approach, the findings of study 1 related to MDD symptoms cannot be generalized to MDD patient samples. Moreover, as previously outlined, due to the temporal order, a pathway with CT alterations as mediator between ELS and future symptomatology might likewise be applicable. In general, future studies should address this issue by collecting longitudinally structural and functional MRI from infancy into early adulthood in large community samples to clarify the proposed pathways. While already controlling for several important confounders, future studies are needed to investigate further mechanism, for instance genetic make-up, hormonal markers, or adult environments, connecting ELS to behavioral and neural abnormalities.

Study 2 focused on the predictive value of prefrontal control on stress burden during a pandemic. While our results highlight the importance of adaptive coping to an unprecedented stressor in general, some limitations need to be mentioned. Since the pandemic started during an ongoing regular assessment wave within the framework of the Mannheim Study of Children at Risk, study 2 was not able to include the complete sample, therefore limiting the results to only those who already participated in the regular wave. Thus, given the distribution of participants of each initial group (i.e., no, low, and high psychosocial risk), the findings might still represent core characteristics of the entire sample. Further, as the COVID-19 baseline assessment started around four weeks after the initial lockdown in Germany, the possibly first and most threatening shock might not be captured by the survey. Moreover, while study 2 investigated the predictive value of coping mechanisms assessed prior to the stressor, additional measurements of distinct coping strategies after the onset would be particularly needed to support the proposed model. While some studies using self-report data on coping styles support our findings (Groarke et al., 2020; Gubler et al., 2020; Rubaltelli et al., 2020), further implicit measures would be of high value. Finally, while a natural stressor directly affecting the whole sample dramatically increases the ecological validity of an

investigation, replications of our findings are most likely impossible. However, our results might act as a starting point and inspire future prevention strategies in response to global health threats.

3.2 Outlook

Although study 1 highlighted infancy as a highly sensitive period for the long-term impact of ELS on prefrontal brain alterations, further longitudinal studies are particularly needed to replicate and confirm our findings. It would be of high interest to use neuroimaging data over the life course, starting as early as possible, to unravel the relationship of brain maturation and the impact of environmental adversities at different developmental stages. Prospectively and objectively collected data is especially warranted in early years of life to prevent recall-bias, and to avoid re-traumatization in participants exposed to severe traumatic events. In addition, it would be of major importance to extend our findings to clinical MDD samples. In a recent study in infants aged 3 months, functional connectivity alterations between the amygdala and parts of the salience and the executive control network mediated the effect of maternal postpartum depression on the infants emotional responsivity (Phillips et al., 2021), providing preliminary evidence for prognostic neural markers to identify those who are at increased risk for developing mental health impairments in later life. Given the high numbers of postpartum depression (Halbreich & Karkun, 2006; Segre et al., 2007), children exposed to maternal MDD and their mothers might be an important target group to longitudinally study the interplay of environmental adversity in infancy, brain maturation and psychopathology.

In addition, personal and interpersonal resilience factors should be further explored and included in a model of the above-mentioned associations of brain trajectories and adverse events. This approach would help to clarify why some individuals exposed to adverse conditions develop mental illness, while others remain spared from mental health

impairments. In this context, assessing and improving individual coping strategies, such as emotion regulation or inhibitory control, might be promising to reduce the impact of environmental threats to an individual's mental and physical health across the life span. Specific early teaching programs to foster coping with life stress administered not only to children at risk but for instance embedded in regular school subjects (Diamond et al., 2007) might help children to grow into mentally robust and resilient adults. Moreover, given the tremendous technological advances in recent years, participation in such coping strategy training programs becomes more and more easy and affordable and can be delivered to a majority of potential participants via smartphone or tablet.

4 SUMMARY

The present thesis addresses the complex interplay of environmental adversities, psychopathology, neural development, and coping mechanisms in a longitudinal at-risk cohort study following its participants since birth.

Specifically, in study 1, we investigated the long-term impact of life stress at different developmental stages, namely infancy, childhood, and adolescence, on prefrontal brain alterations. Therefore, life stress was recorded in regular intervals starting at the age of 3 months until the age of 25 years by reporting chronic and adverse life events occurring not more than one year prior to the assessment time point. Structural brain imaging was conducted at the age of 25 years. Moreover, depressive symptoms were assessed in young adulthood via self-report. In a sample of 190 healthy adults, increased exposure to life stress in infancy predicted cortical thickness reductions in the orbitofrontal cortex, a key region for affective processing. Neither life stress in childhood nor in adolescence was further related to abnormal brain development. Moreover, increased depressive symptoms in young adulthood were found in those previously exposed to life stress in infancy, and predicted cortical thickness reductions in later life. Finally, a mediation model revealed that depressive symptoms partially mediated the impact of life stress in infancy on abnormal brain maturation in the orbitofrontal cortex at the age of 25 years.

Study 2 investigated the predictive value of coping strategies in response to a natural stressor. In more detail, emotion regulation and inhibitory control were assessed in 104 participants during functional neuroimaging prior to the COVID-19 crisis, an unprecedented global stressor affecting physical and mental health. Stress burden due to the pandemic was recorded at three time points during the course of the crisis, that is four weeks after the initial lockdown during the first wave of the pandemic, then during the summertime when

restrictions loosened and infection rates went down, and finally at the beginning of the second wave of the pandemic in late 2020 when case numbers exponentially increased. Higher neural activity in the inferior frontal gyrus during emotion regulation predicted less stress burden in consequence of the crisis at the first and second wave of the pandemic, whereas enhanced neural activity of the medial frontal gyrus during inhibitory control predicted diminished stress levels during the summer. These findings hold true after controlling for several important confounders, which were previously linked to stress responsivity. Therefore, adequate emotion regulation is particularly needed in the face of first-level threats, such as emotional distress and acute socio-affective challenges, which were caused by the immediate changes in everyday life at the beginning of the crisis when social contact restrictions were initially installed. In contrast, we propose that effective usage of inhibitory control is required in response to second-level threats, such as dealing with ongoing socio-economic challenges, which were present during the summer.

Taken together, our findings highlight the long-term impact of early life stress during infancy on brain structure in adults and point to a critical involvement of internalizing psychopathology. Given the high rates of early life adversities in clinical samples, future prevention strategies are particularly needed to overcome those long-term consequences. In addition, our findings emphasize the importance of effective coping mechanisms, such as adequate emotion regulation and inhibitory control, in response to a natural stressor. Therefore, we suggest early, easy to reach and affordable interventions delivered via smartphone or tablet to foster coping strategies in everyday life.

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