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The long-term impact of childhood adversities on brain function and connectivity

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PREFACE

This work is a cumulative dissertation based on empirical studies. Study I and Study II were published in peer-reviewed journals. Study III is currently in Revision in a peer-reviewed journal. The section “Empirical Studies” incorporates the theoretical basis of the empirical works and related methods, results, and discussion sections. These sections, including the tables and figures, are identical to the published works.

These empirical studies are listed below.

Publication 1: Sacu, S., Dubois, M., Hezemans, F.H., Aggensteiner, P-M., Monninger, M., Brandeis, D., Banaschewski, T., Hauser, T., & Holz, N.E. (2024). Early life adversities are associated with lower expected with lower expected value signaling in the adult brain. Biol. Psychiatry.

The corresponding chapter in the dissertation is **2.1 Study I: Early life adversities are associated with lower expected with lower expected value signaling in the adult brain**.

Publication 2: Sacu, S., Aggensteiner, P-M., Monninger, M., Brandeis, D., Banaschewski, T., & Holz, N.E. (2024). Lifespan adversities affect neural correlates of behavioral inhibition in adults. Front Psychiatry.

The corresponding chapter in the dissertation is **2.2 Study II: Lifespan adversities affect neural correlates of behavioral inhibition in adults**.

Publication 3: Sacu, S., Hermann, A., Banaschewski, T., Gerchen, M.F., & Holz, N.E. (2024). The long-term correlates of developmental stress on whole-brain functional connectivity during emotion regulation. In Review in *Translational Psychiatry*.

The corresponding chapter in the dissertation is **2.3 Study III: The long-term correlates of developmental stress on whole-brain functional connectivity during emotion regulation**.

Data used for the publications were collected between 1986 and 2021. I did not contribute to study design, ethics approval and data collection. My contributions included the conceptualization of research questions (based on previously-collected data and current literature), conducting data analysis, interpreting and visualizing the results, writing and editing the manuscripts, and managing the submission and revision processes for peer-reviewed journals. A summary of my contributions can be found in the table below.

Work steps	**Publication 1**	**Publication 2**	**Publication 3**
Conception (%)	20%	20%	20%
Literature search (%)	100%	100%	100%
Ethics proposal (%)	0%	0%	0%
Animal experimentation proposal (%)	NA	NA	NA
Data collection (%)	0%	0%	0%
Data analysis (%)	65%	85%	85%
Interpretation of results (%)	65%	80%	80%
Manuscript writing (%)	65%	70%	70%
Revision (%)	65%	80%	Ongoing
Indicate which figures and tables resulted from your dissertation work.	Figure 1-5 (Figure 2-6 in the dissertation) Table 1 (Table 1 in the dissertation)	Figure 1-5 (Figure 7-11 in the dissertation) Table 1-2 (Table 2-3 in the dissertation)	Figure 1-3 (Figure 12-14 in the dissertation) Table 1 (Table 4 in the dissertation)

LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
AIC	Akaike Information Criterion
ASR	Adult Self-Report
BIC	Bayesian Information Criterion
CTQ	Childhood Trauma Questionnaire
dACC	Dorsal Anterior Cingulate Cortex
DAN	Dorsal Attention Network
DMN	Default Mode Network
EF	Executive Functions
ELS	Early Life Stress
EV	Expected Value
FDR	False Discovery Rate
FPN	Frontoparietal Network
FWE	Familywise Error
IFG	Inferior Frontal Gyrus
MCC	Middle Cingulate Cortex
mPFC	Medial Prefrontal Cortex
MTG	Middle Temporal Gyrus
NAcc	Nucleus Accumbens
NBS	Network-Based Statistics
PE	Prediction Error
pgACC	Pregenual Anterior Cingulate Cortex
SMA	Supplementary Motor Area
SN	Salience Network
vmPFC	Ventromedial Prefrontal Cortex

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1 INTRODUCTION

Exposure to childhood adversities is an important public health concern that has long-lasting consequences on physical and mental health (K. Hughes et al., 2017). Despite the lack of consistency in definition and measurement, adversities generally refer to severe or chronic events, which reflect deviations from an expected environment and require significant adaptation by an average child (McLaughlin, 2016). Maltreatment (e.g., abuse and neglect), household dysfunction (e.g., parental psychopathology, domestic violence), economic hardship, and community violence can be only a few examples of adversities that children might experience while growing up (Cronholm et al., 2015; Felitti et al., 1998).

Exposure to childhood adversities is prevalent, affecting approximately 30-50% of the population according to the findings of large epidemiological studies (Fujiwara & Kawakami, 2011; Green et al., 2010; Kessler et al., 2010; Lee et al., 2011; Slopen et al., 2010). They have a detrimental effect on health and well-being (Hales et al., 2023; K. Hughes et al., 2017). An extensive body of research has shown that adverse childhood experiences are associated with a higher risk of developing mental health problems, such as depression, substance abuse, and suicide attempts, and a higher incidence of physical illnesses, such as coronary heart disease, diabetes, and obesity (Felitti et al., 1998; Felitti, 2002; C. M. Jones et al., 2020; Merrick et al., 2017). Importantly, these associations are dose-dependent. The risk for negative health outcomes increases as the number of exposure increases (Felitti et al., 1998; Felitti, 2002; C. M. Jones et al., 2020; Merrick et al., 2017) and their impact persists across the life course (Green et al., 2010; Raposo et al., 2014; Sacu, Aggensteiner, et al., 2024; Sacu, Dubois, et al., 2024).

Moreover, adversities alter brain development (K. E. Smith & Pollak, 2020). Neuroimaging studies have consistently reported neural alterations following childhood adversities (Bick & Nelson, 2016; Vaidya et al., 2024), which can also potentially mediate the relationship between adversities and health outcomes. Enriched environments (e.g., multi-sensory stimulation, social interactions) can provide an optimal environment for healthy brain development (Han et al., 2022). Deviations from an optimal environment, such as lack of required input/proper stimulation (e.g., neglect, institutionalization) or presence of undesirable conditions (e.g., abuse, violence) might interrupt normal brain development (Chan et al., 2024; McLaughlin, 2016; Tooley et al., 2021). Indeed, a large body of research has established that childhood adversities impact the brain, including structure (Holz, Zabihi, et al., 2023; Pollok et al., 2022), function (Hosseini-Kamkar et al., 2023; Kraaijenvanger et al., 2020) and connectome (Kraaijenvanger et al., 2023).

In addition, although empirical studies identified similar adversity-related brain changes across development (McLaughlin, Weissman, et al., 2019), studies disentangling the developmental effects based on measurement time yielded conflicting results. For example, a previous meta-analysis investigated adversity-related changes in brain functioning across different task domains and identified increased amygdala activation and lower prefrontal cortex activation in adults. In contrast, no such effects were identified for children and adolescents (Hosseini-Kamkar et al., 2023). Another meta-analysis examining adversity-related structural changes reported distinct effects based on age-group (Pollok et al., 2022). Right amygdala and hippocampus emerged as a convergence site for children and adolescents, while pregenual anterior cingulate cortex was appeared as a convergence site for adults. On the other hand, a recent longitudinal study identified

stable structural changes across adulthood (Holz, Zabihi, et al., 2023). Inconsistent results might be due to possible confounds, such as measurement domain (e.g., function, structure), experimental task (e.g., reward processing, emotion processing), timing of adversity, severity and duration of exposure, and other sample characteristics (e.g., healthy, clinical). Therefore, longitudinal neuroimaging studies encompassing lifespan development are needed to disentangle adversity–related developmental effects.

In terms of brain functioning, exposure to childhood adversities is associated with alterations in brain systems related to reward processing, cognitive control, and emotion regulation (Bick & Nelson, 2016; Holz, Berhe, et al., 2023; McLaughlin, Weissman, et al., 2019; Vaidya et al., 2024). Previous studies provided evidence for reduced striatal activation during reward anticipation (Birn et al., 2017; Boecker et al., 2014; Holz et al., 2017; Mehta et al., 2010), altered prefrontal activation during inhibitory control (Bruce et al., 2013; Demers et al., 2022; Holz et al., 2014; Lees et al., 2020; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015) and impaired regulatory control of limbic regions (Dannlowski et al., 2013; Herringa et al., 2016; Javanbakht et al., 2015; Kim et al., 2013) in individuals exposed to adversities. In addition, meta-analytic research identified similar neural alterations in terms of reward processing (Feng et al., 2022), inhibitory control (Yan et al., 2022) and emotion regulation (McTeague et al., 2020) across different psychiatric disorders, including depressive disorders, anxiety, schizophrenia and substance use, which indicates a transdiagnostic mechanism. Given that both individuals exposed to adversities (Bick & Nelson, 2016; McLaughlin, Weissman, et al., 2019; Tyrka et al., 2013) and individuals with different psychopathologies (Feng et al., 2022; McTeague et al., 2020; Yan et al., 2022) showed similar alterations in these brain systems, these neural changes following adversity

exposure can play a mediator role in the adversity-psychopathology relationship (Holz et al., 2015; McLaughlin, DeCross, et al., 2019). Therefore, identifying neurodevelopmental pathways linking adversity with psychopathology is crucial to establish treatment targets and prevent mental health problems among the individuals exposed to adversities (Holz et al., 2015; McLaughlin, DeCross, et al., 2019).

The current dissertation aimed to investigate the long-term impact of childhood adversities on the brain and behavior. In specific, we are interested in associations between adversities and brain functioning in the context of reward-based decision making, executive functioning and emotion regulation. We additionally aimed to examine if adversity-related neural alterations can explain behavior (e.g., psychopathology symptoms) or play a mediator role in linking adversities with psychopathology symptoms. To provide a comprehensive overview of previous literature, we divided the introduction into five sections. The first three sections provide an overview of evidence how adversities are related to altered reward learning, behavioral inhibition and emotion regulation. The fourth section addresses the current limitations and gaps in the field. The fifth section introduces research questions and discusses how the current dissertation would address the limitations in the field.

1.1 Reward Learning

Developing accurate predictions about future events requires learning from the consequences of a behavior (e.g., reward or punishment). However, behavioral consequences are not always stable in the environment. Therefore, updating the outcome-related beliefs in the presence of novel information is essential to successfully navigate the world (Den Ouden et al., 2012). These two fundamental reinforcement learning processes, forming expectations about choice options— expected value (EV) and updating them based on the discrepancy between expected and actual

outcomes— prediction error (PE), are essential for adaptation, and shape goal-directed human behavior (e.g., avoid or approach) (Chase et al., 2015; Dolan, 2007; Schultz, 2016).

At the neural level, several reward-related brain regions involve in EV and PE signaling, including the striatum (Chase et al., 2015; Dayan & Niv, 2008; Schultz, 2016), ventromedial prefrontal cortex (vmPFC) (Chase et al., 2015; O'Doherty et al., 2007), and anterior cingulate cortex (ACC) (Hyman et al., 2017). Neuroimaging studies further suggested the distinct contribution of these regions in EV and PE signaling. For example, vmPFC is widely associated with EV encoding and subjective reward value (Dolan, 2007; O'Doherty et al., 2007; Peters & Büchel, 2010), while the striatum (Chase et al., 2015; Den Ouden et al., 2012; Yacubian et al., 2006) and ACC (Alexander & Brown, 2019; Hyman et al., 2017; Monosov, 2017) are related to both EV and PE signaling.

Recent literature suggested that exposure to childhood adversities is associated with altered reward-guided behavior (Lloyd et al., 2022; Wilkinson et al., 2021). This might be due to sparsity and randomness of rewards in adverse rearing environments (Novick et al., 2018). Furthermore, a large body of research identified a consistent association between childhood adversities and neural alterations in the reward circuitry, for example, lower striatal (Birn et al., 2017; Boecker et al., 2014; Holz et al., 2017; Mehta et al., 2010) and prefrontal cortex (Birn et al., 2017; Boecker et al., 2014; Casement et al., 2013) activation during reward anticipation. On the other hand, both enhanced (Boecker et al., 2014; Casement et al., 2014; Morgan et al., 2014) and blunted (Hanson et al., 2015, 2016; Takiguchi et al., 2015) striatal responses were observed during reward delivery. However, it is important to note that these studies only examined how neural response to a rewarding stimulus was altered in individuals

exposed to adverse experiences and did not take into account other important information regarding the stimulus, such as probability and magnitude. Computational modelling approaches are necessary to provide a deeper understanding on how adverse experiences influence human choice behavior (O'Doherty et al., 2007).

To date, only a few previous studies investigated how childhood adversities affect reinforcement learning processes using computational neuroimaging approaches. Their results provided evidence for reduced EV (Gerin et al., 2017; Palacios-Barrios et al., 2021) and PE signaling (Cisler et al., 2019) in the reward-related brain regions, including the striatum, vmPFC and ACC. The EV-related neural alterations were further associated with higher anxiety (Gerin et al., 2017) and withdrawn (Palacios-Barrios et al., 2021) symptoms. Reduced neural responses during EV/PE signaling were also identified in several mental health conditions, including depression (C. Chen et al., 2015), anxiety (S. F. White et al., 2017), disruptive behavior disorder (S. F. White et al., 2013) and conduct disorder (S. F. White, Tyler, Erway, et al., 2016). Therefore, neural alterations can reflect a shared mechanism, and might potentially increase the risk of developing psychopathology in individuals with adverse experiences.

1.2 Inhibition

Inhibitory control is a core component of executive functioning and self-regulation (Zelazo, 2020). It refers to the ability to suppress a behavior when responding is no longer necessary or inappropriate (Diamond, 2013), and consists of several distinct components, such as inhibiting a preplanned motor response or overcoming conditioned responses/habits (Kang et al., 2022). At neural level, enhanced recruitment of frontal regions, such as inferior frontal gyrus (IFG) and supplementary motor area (SMA), were consistently reported during successful inhibition (Aron &

Poldrack, 2006; Cai et al., 2014; Korucuoglu et al., 2021; Rubia et al., 2003; Steele et al., 2013). Increased dorsal ACC activation in response to failed inhibition was also observed in several studies (Duann et al., 2009; Korucuoglu et al., 2021; Rubia et al., 2003), potentially reflecting error processing (Dali et al., 2023).

Previous work identified executive functioning difficulties in individuals exposed to adverse environments (Lund et al., 2020, 2022). In line with this, individuals exposed to adversities exhibited altered activation in frontal brain regions during inhibitory control tasks (Bruce et al., 2013; Demers et al., 2022; Holz et al., 2014; Lees et al., 2020; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015). However, the direction of the alterations was specific to the experimental paradigm used. Enhanced activation of frontal regions was observed in the studies using the stop-signal task (Lees et al., 2020; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015), while the reverse pattern was present in the studies using the Go/No Go task (Bruce et al., 2013; Demers et al., 2022; Holz et al., 2014). Although both tasks were commonly used to measure response inhibition, they might involve distinct mechanisms, namely action restraint and action cancellation (Raud et al., 2020), which can explain conflicting findings.

Furthermore, executive functioning impairments (Snyder et al., 2015, 2019) and altered activation in frontal regions during inhibitory control (Bartholdy et al., 2019; Malejko et al., 2021; Massat et al., 2018; Nixon et al., 2013; E. J. White et al., 2023) were documented in several mental health conditions, indicating a transdiagnostic mechanism. Given the similar neural changes between adversities and mental health conditions, altered frontal cortex activation during inhibitory control can reflect a neural vulnerability marker, which might increase the risk of developing psychopathology in individuals exposed to childhood adversities.

1.3 Emotion Regulation

The ability to regulate emotions is an important aspect of mental well-being, which is associated with several adaptive outcomes in daily life, including down-regulation of negative feelings, avoiding social conflicts, and gaining perceived control over the situations (Wilms et al., 2020). Although several strategies (e.g., acceptance, distraction, suppression, rumination) are available to regulate emotions, cognitive reappraisal is one of the most studied strategies in the research context (Naragon-Gainey et al., 2017). It involves reinterpretation of a situation and is found be effective with desired changes in self-reported emotion (McRae & Gross, 2020).

Studies investigating neural correlates of cognitive reappraisal revealed that cognitive control regions, such as frontal and parietal regions, increase their activation during emotion regulation, while the activation of limbic regions (e.g., amygdala, insula) decreases (Buhle et al., 2014; Kohn et al., 2014). In addition, altered connectivity between amygdala and frontal regions during emotion regulation was repeatedly reported across the seed-based functional connectivity studies (Berboth & Morawetz, 2021; Di et al., 2017), potentially reflecting the modulation of amygdala by frontal regions.

Individuals exposed to adversities often present with emotion regulation difficulties (Weissman et al., 2019). Brain regions involved in emotion regulation are also found to be altered in these individuals. Especially, enhanced amygdala activation to negative stimuli (Dannlowski et al., 2013; Javanbakht et al., 2015; Kraaijenvanger et al., 2020) and altered connectivity between amygdala and frontal regions (Holz, Berhe, et al., 2023; Kim et al., 2013; Kraaijenvanger et al., 2023) were consistently identified in individuals with adverse childhood experiences, even several years after the exposure. Taken together, these findings suggest that altered activity and

connectivity of frontal and limbic regions during emotion regulation can be a neural phenotype of childhood adversities and might reflect less efficient modulation of amygdala by frontal regions.

Although fronto-limbic connectivity plays a crucial role in emotion regulation and stress-related psychopathologies (VanTieghem & Tottenham, 2018), we know less about how global or whole-brain connectivity is altered following early life stress (Holz, Berhe, et al., 2023). Previous research suggested that several large-scale brain networks can involve in emotion regulation beyond the fronto-limbic pathway, including salience network (attention allocation, implicit emotion regulation), executive control networks (goal-directed behavior) and default-mode network (mentalizing, memory) (Barrett & Satpute, 2013; Morawetz et al., 2020). Thus, investigating whole-brain connectivity change via large-scale brain networks can bring new insights into the neural embedding of early life stress.

Moreover, a recent study reported that childhood abuse, not adolescent abuse, was related to intrinsic connectivity alterations across several large-scale networks in adults (Korgaonkar et al., 2023), underscoring the importance of the developmental timing of stress in adult brain organization. However, this study could not address the impact of adversities occurring very early in life (i.e., adversities occurring under the age of three) due to its retrospective nature. Although several previous studies examined the effect of early life stressors (e.g., prenatal stress) on brain connectivity (Brady et al., 2022; De Asis-Cruz et al., 2020; Qiu et al., 2015; Smyser et al., 2010), their samples were limited to infants. Recently, one study investigated the impact of prenatal stress (e.g., maternal anxiety) on resting-state functional connectivity in adults using a longitudinal design (Turk et al., 2023). However, to date, no previous study has

investigated the impact of lifespan stress (i.e., stress occurring at different developmental stages in a large temporal spectrum) on adult brain connectivity yet.

1.4 Literature Gaps

Decades of research have shown that adverse childhood experiences have a lasting impact on physical health, mental well-being and brain organization. However, there are still important gaps in the literature that need to be addressed. First, adversities tend to occur together (Holz, Berhe, et al., 2023), however, most of the previous studies investigating neural underpinnings of childhood adversities focused on a single type of adversity, ignoring the cumulative effects. The cumulative risk approach creates a risk score based on the occurrence of distinct forms of adversity and has several advantages in the context of adverse childhood experiences (McLaughlin, Weissman, et al., 2019). It offers a realistic framework, provides greater statistical power, and prevents overestimating the effect of a single adversity (Evans et al., 2013). However, it has also limitations. It treats each adversity equally, assuming that their impact is equal and can be summed (McLaughlin, 2016). This assumption might be problematic in some cases since severity, duration, or chronicity is not equivalent across the adversities (Bhutta et al., 2023). Therefore, it might be important to take into account the specificity of adversities (McLaughlin, 2016).

There are data-driven statistical approaches, which account for the correlated nature of adversities while providing specificity (Vaidya, 2024). For example, factor analysis can reduce the dimension of data and create meaningful components providing specificity to some extent at the level of broader factors rather than individual adversities. This approach is already successfully applied in behavioral (Afifi et al., 2020; Green et al., 2010) and neuroscientific (Holz, Zabihi, et al., 2023; Sacu, Aggensteiner, et al., 2024; Sacu, Dubois, et al., 2024) stress research. This broader

perspective can help in understanding general patterns of cumulative risk and their potential influence on long-term development. However, it is important to acknowledge that factor analysis might not fully account for the temporal dynamics or the specific, time-sensitive effects of individual adversities

Second, there is a growing interest in examining sensitive periods for stress exposure. A sensitive period suggests that stress occurring at different stages of life might have different impacts on a neural system of interest (Y. Chen & Baram, 2016). The human brain is highly plastic, experiencing the most rapid development early in life but continues to mature across development (Dufford et al., 2021). Given the dynamic changes in neuroplasticity, the effect of adversities on the brain and behavior might vary according to the developmental stages in which adversity occurs. However, since the pace of brain maturation is not identical across different brain regions, the timing of the sensitive period is also expected to differ according to neural circuits (Gee & Casey, 2015).

To date, several studies provided evidence for sensitive periods in terms of mental health outcomes (Dunn et al., 2020; Khan et al., 2015), brain structure (Siehl et al., 2022; Teicher et al., 2018), brain function (Zhu et al., 2019), and brain connectivity (Korgaonkar et al., 2023). However, there are some important challenges for studying sensitive periods for stress exposure. First, it intrinsically requires developmental variation in stress exposure (Bhutta et al., 2023). Second, most of the above-mentioned studies measured childhood adversities retrospectively, which might introduce recall bias and be less likely to address the impact of adversities that occurred very early in life (e.g., first three years).

Lastly, there are only a few longitudinal neuroimaging studies showing the lasting impact of prospectively collected adversities on the adult brain. Some adversity-related

alterations are stable across the life course (Holz, Zabihi, et al., 2023), while other alterations can be short-term or reversible (Gunnar & Bowen, 2021). Moreover, some effects might manifest themselves later in life (Bick & Nelson, 2016). Although the reorganization of the brain in response to adverse environments might be adaptive in the short term (Gee et al., 2013; Gee & Casey, 2015), long-term consequences can be disruptive. Therefore, investigating long-term associations between adverse childhood experiences, adult brain organization and mental health outcomes will bring additional insights and complement the previous cross-sectional research.

1.5 Aims and Hypotheses

The current thesis investigated long-term associations between childhood adversities and adult brain functioning. We aimed to provide a more comprehensive view by taking into account cumulative effects, considering sensitive periods (in terms of long-term associations), and extending the investigation into adulthood. For this purpose, we used data from a longitudinal birth cohort study, Mannheim Study Children at Risk. The study was designed to investigate the long-term effect of biological and psychosocial risk factors on development (Laucht et al., 2000). All participants were followed since their birth up to 33 years across 11 assessment waves. Several measures in different domains were collected during these assessment waves, including risk factors, psychopathology, biomarkers (e.g., genetics, endocrinology), cognitive and social development measures, and neuroimaging assessments from young adulthood on. For the current dissertation, we used functional MRI assessments during adulthood and adversity measures collected across development. To show how adversity-related neural changes were related to mental health outcomes, we used psychopathology measures collected at the time of fMRI assessment and during the COVID-19 pandemic. See Figure 1 for the measurements used for the current dissertation.

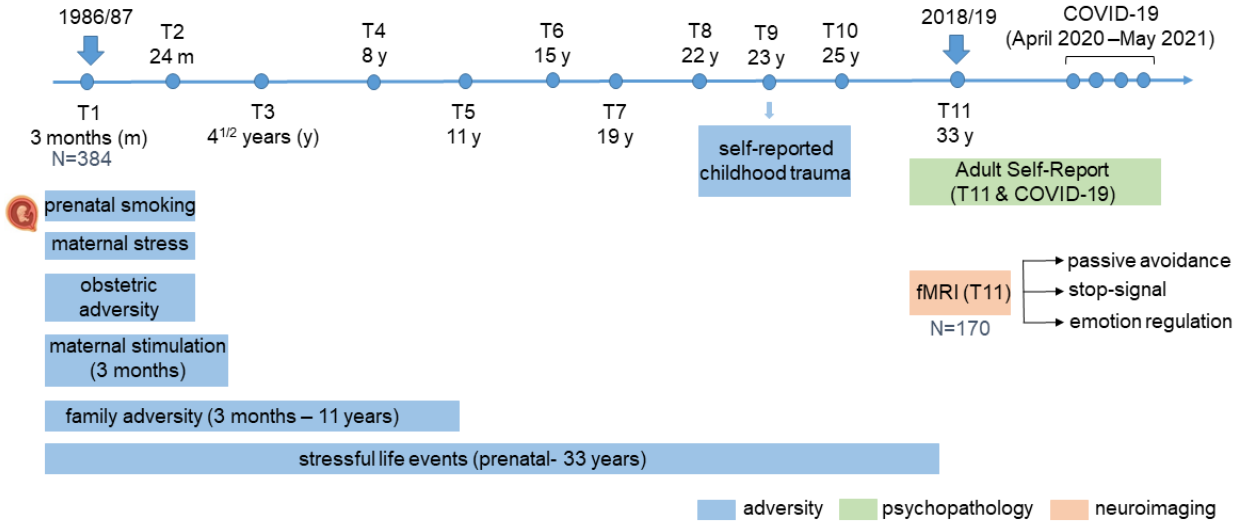

Figure 1. Graphical summary of measurements.

Study I and Study II used multiple adversity measures covering prenatal (e.g., maternal stress, maternal smoking), perinatal (e.g., obstetric adversity) and postnatal (e.g., lower maternal stimulation, family adversity, stressful life events, and childhood trauma) periods. It is important to note that these adversity measures, except the self-reported childhood trauma, were prospectively collected and reflect exposures rather than subjective experiences. To reduce dimensionality and address the co-occurrence of adversities, we applied principal component analysis, which resulted in a three-factor solution (factor 1: postnatal psychosocial adversities and prenatal maternal smoking, factor 2: prenatal maternal stress and obstetric adversity, and factor 3: lower maternal stimulation). We then investigated how these adversity factors, as well as specific adversity measures, were associated with neural correlates of reinforcement learning and behavioral inhibition, respectively. Since some of the measures were collected prospectively at multiple time points (e.g., family adversity and stressful life events), we conducted exploratory analyses with time-specific adversity measures to address sensitive periods. However, these results should be considered preliminary due to the high number of testing.

Study III examined the associations between the developmental timing of stress and task-based functional connectivity during an emotion regulation task. As an adversity measure, we used stressful life events (Maier-Diewald et al., 1983). To represent developmental stages, we used the following sum scores: prenatal period and newborn (from pregnancy to up to postnatal 3 months), infancy and toddlerhood (three months to 4.5 years), childhood (4.5 years to 11 years), and adolescence (11 years to 19 years). Task-based whole-brain functional connectivity was calculated during emotion regulation using whole-brain generalized psychophysiological interactions (Gerchen et al., 2014).

1.5.1 Study I Hypotheses

Study I aimed to investigate the effect of childhood adversities on reinforcement learning processes (i.e., EV/PE signaling) using the passive avoidance task. Based on previous research (Cisler et al., 2019; Gerin et al., 2017; Palacios-Barrios et al., 2021), we hypothesized that childhood adversities (e.g., adversity factors and specific adversity measures) would be associated with lower EV and PE encoding in the striatum, ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC). Furthermore, we hypothesized that lower EV and PE encoding in these regions would be associated with higher psychopathology symptoms in adulthood.

1.5.2 Study II Hypotheses

Study II aimed to investigate associations between lifespan adversities and neural correlates of inhibitory control using the stop-signal task. We hypothesized that the adversities across development (e.g., adversity factors and specific adversity measures) would be associated with increased functional activation in several frontal regions during inhibitory control, including the inferior frontal gyrus (IFG), pre-supplementary motor area (pre-SMA), and dorsal anterior cingulate cortex (dACC).

Furthermore, altered frontal activation would be associated with lower inhibition success and higher psychopathology symptoms in adulthood.

1.5.3 Study III Hypotheses

Study III aimed to investigate the impact of developmental life stress on functional connectivity during an emotion regulation task. We hypothesized that early life stress would be associated with alterations in networks related to emotion processing and cognitive control, including salience, limbic, and frontoparietal networks (Herzberg et al., 2021). We did not put forward a specific hypothesis regarding the direction of changes because of scarce evidence. In addition, we expected to see that these network alterations would be linked to psychopathology (e.g., higher internalizing and externalizing symptoms).

2 EMPIRICAL STUDIES

2.1 Study I: Early life adversities are associated with lower expected value signaling in the adult brain

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https://doi.org/10.1016/j.biopsych.2024.04.005

2.1.1 Abstract

Early adverse experiences are assumed to affect fundamental processes of reward learning and decision-making. However, computational neuroimaging studies investigating these circuits in the context of adversity are sparse and limited to studies conducted in adolescent samples, leaving the long-term effects unexplored. Using data from a longitudinal birth cohort study (n=156, 87 females), we investigated associations between adversities and computational markers of reward learning (i.e., expected value (EV), prediction errors). At the age of 33 years, all participants completed an fMRI-based passive avoidance task. Psychopathology measures were collected at the time of fMRI investigation and during the COVID-19 pandemic. We applied a principal component analysis to capture common variation across seven adversity measures. The resulting adversity factors (factor-1: postnatal psychosocial adversities and prenatal maternal smoking, factor-2: prenatal maternal stress and obstetric adversity, and factor-3: lower maternal stimulation) were linked with psychopathology and neural responses in the core reward network using multiple regression analysis. We found that the adversity dimension primarily informed by lower maternal stimulation was linked to lower EV representation in the right putamen, right nucleus accumbens (NAcc), and anterior cingulate cortex. EV encoding in the right NAcc further mediated the relationship between this adversity dimension and psychopathology and predicted higher withdrawn symptoms during the COVID-19 pandemic. Our results suggested that early adverse experiences in caregiver context might have a long-term disruptive effect on reward learning in reward-related brain regions, which can be associated with suboptimal decision-making and thereby may increase the vulnerability of developing psychopathology.

2.1.2 Introduction

Being able to adapt and learn about one's environment is critical for successfully navigating the world (Dolan, 2007). Developing accurate predictions about future events and updating them based on novel information becomes especially important in dynamic environments where constant change is present (Den Ouden et al., 2012). However, these fundamental processes of feedback learning have been found to be impaired across a range of mental disorders (Hauser et al., 2014; Zald & Treadway, 2018). Early adverse environments are also believed to alter reinforcement learning processes as inconsistencies in feedback contingencies (Novick et al., 2018) and suboptimal conditions for neurocognitive development (Gee et al., 2018) are prevalent in adverse rearing environments.

Reinforcement learning constitutes that humans form expected values (EV) about choice options and update them based on prediction errors (PE) (Chase et al., 2015). PE occurs when there is a discrepancy between the expected and actual outcomes, and serves as a teaching signal by allowing the organism to update the EV of future events (Schultz, 2016). At the neural level, several brain regions were found to involve in EV and PE signaling including the striatum (Chase et al., 2015; Dayan & Niv, 2008; Schultz, 2016), ventromedial prefrontal cortex (Chase et al., 2015; O'Doherty et al., 2007), anterior cingulate cortex (Hyman et al., 2017), and amygdala (Dayan & Niv, 2008; Dolan, 2007). Lower EV/PE signaling in these regions has also been identified in several psychiatric conditions, including both internalizing disorders such as depression (C. Chen et al., 2015) and anxiety (S. F. White et al., 2017) and externalizing disorders such as disruptive behavior disorder (S. F. White et al., 2013) and conduct disorder (S. F. White, Tyler, Erway, et al., 2016).

Several neuroimaging studies have reported a relationship between adverse experiences and alterations in the reward circuitry (Birn et al., 2017; Blair et al., 2022; Boecker et al., 2014; Hendrikse et al., 2022; Holz et al., 2017), however, research investigating this using computational neuroimaging approaches remains scarce. Computational neuroimaging brings new insights by taking into account other important information regarding the stimulus (e.g., probability, magnitude), which allows modeling the cognitive process beyond the simple stimulus-response relationship (O'Doherty et al., 2007). To date, only a few previous studies investigated the association between early adverse experiences and EV/PE signaling. These studies reported evidence for reduced EV (Gerin et al., 2017; Palacios-Barrios et al., 2021) and PE signaling (Cisler et al., 2019) in individuals exposed to adversities, suggesting that adversities may indeed affect reinforcement learning processes. However, these studies included only single measures of adversity (Cisler et al., 2019; Gerin et al., 2017; Palacios-Barrios et al., 2021), despite the fact that adversities tend to co-occur and accumulate over time (Holz, Berhe, et al., 2023). Therefore, a comprehensive approach encompassing cumulative effects is needed to investigate the effect of diverse adverse experiences on reinforcement learning. In addition, these studies measured the brain responses only during adolescence (Cisler et al., 2019; Gerin et al., 2017; Palacios-Barrios et al., 2021), leaving the long-term effects of developmental risks on EV/PE signaling in the adult brain largely unexplored. Lastly, the retrospective design of many studies limits insights into the specific developmental periods when adversities occur (Cisler et al., 2019; Gerin et al., 2017). Our study seeks to address these gaps by considering a broader range of adversities and extending the investigation into adulthood, thus offering a more complete picture of the long-term neural consequences of early life adversities.

Here, we aimed to investigate the effect of a lifespan adversity profile on reward-related brain functioning (i.e., EV/PE signaling) and mental health in adulthood in a cohort of participants followed since birth. Risk measures were collected across the development and included prenatal, perinatal, and postnatal factors (Holz, Zabihi, et al., 2023). All participants completed an fMRI-based reinforcement learning paradigm and psychopathology measures at the age of 33 years. Based on previous research (Cisler et al., 2019; Gerin et al., 2017; Palacios-Barrios et al., 2021), we hypothesized that adverse experiences would be associated with lower EV and PE encoding in the striatum, ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC). Furthermore, we hypothesized that lower EV and PE encoding in these regions would be associated with higher psychopathology symptoms in adulthood.

2.1.3 Methods and Materials

2.1.3.1 Participants

The present study was conducted in the framework of the Mannheim Study of Children at Risk, which is an ongoing longitudinal birth cohort study. The initial sample included 384 children born between 1986 and 1988. The participants were followed from their birth up to around the age of 33 years across 11 assessment waves. At the last assessment wave (T11), 170 participants had fMRI data for the passive avoidance task. After the quality check (Supplementary Material S1 for exclusion criteria and attrition analyses), the sample size was reduced to 156 participants (Table 1). At the time of the fMRI assessment, 22 (14%) participants had current psychopathology, which was assessed using the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997). The study was approved by the ethics committee of the Heidelberg University. All participants gave informed consent.

Table 1. Study I sample characteristics.

	N=156
Age, M(SD)	32.4(0.4)
Sex, N, F/M	87/69
Maternal Smoking, N, non-/moderate/heavy smoker	116/17/23
Maternal Stress, M(SD), range	2.8(1.9), 0-8
Obstetric Adversity, N, no/moderate/high risk	62/83/11
Maternal Stimulation [a], M(SD), range	0.31(2.4), 6-7.2
CTQ total, Median(IQR), range	28(6), 25-87
Family Adversity [b], M(SD), range	3.5 (2.3), 0-10
Stressful Life Events [c], M(SD), range	0(6), -11.2-22.2
Internalizing Symptoms, Median(IQR), range	5(8), 0-40
Externalizing Symptoms, Median(IQR), range	7(12), 0-45
ADHD, Median(IQR), range	4(6),0-24
Antisocial Personality, Median(IQR), range	2(3),0-19
Anxiety, Median(IQR), range	3(4),0-9
Avoidant Personality, Median(IQR), range	1(4), 0-11
Depression, Median(IQR), range	2(5), 0-19
Somatic Problems, Median(IQR), range	1(2), 0-11

[a] We used reversely-coded z-transformed scores. Higher scores indicated lower maternal stimulation.
[b] Family adversity reflected the sum score of 11 adverse family factors up to 11 years.
[c] We used the sum score of z-transformed total scores across the 11 assessment waves.

2.1.3.2 Psychological Measurements

2.1.3.2.1 Lifespan Adversity

All risk measures were carefully selected based on their impact on psychosocial and psychopathological development (Birn et al., 2017; Boecker et al., 2014; Entringer et al., 2015; Gerin et al., 2017; Laucht et al., 2000; Morgan et al., 2014; Muller et al., 2013; Zohsel et al., 2014). For the prenatal period, we included maternal stress (Zohsel et al., 2014) and maternal smoking (Holz et al., 2014). Obstetric adversity was included

as a measure of perinatal risk (Laucht et al., 2000). Postnatal measures included maternal stimulation during infancy, family adversity up to 11 years (Laucht et al., 2000), and stressful life events over the lifespan (Maier-Diewald et al., 1983) and childhood trauma questionnaire (Wingenfeld et al., 2010). Detailed descriptions can be found in Supplementary Material S2.

To reduce the dimensionality while also accounting for the interrelatedness of the adversity measures (Table S3), we applied principal component analysis using the above-mentioned adversity measures (Afifi et al., 2020; Green et al., 2010; Holz, Zabihi, et al., 2023; Mersky et al., 2017). We identified three components with an eigenvalue > 1, which in total explained 66.8% of the variance in the data (See details in Results).

2.1.3.2.2 Psychopathology

We used the Adult Self-Report (Achenbach & Rescorla, 2003) to assess current symptoms of psychopathology. Internalizing and externalizing problems scores were used to probe if general psychopathology scores are associated with adversity factors. Due to non-normally distributed data, Spearman's correlation test was performed. P values were adjusted for multiple comparisons using false discovery rate (FDR) correction. If we identified a significant association, we further explored if a specific subscale contributed to this association using the ASR subscales (depression, anxiety, avoidant personality, somatic problems, attention deficit and hyperactivity disorder, and antisocial personality). Results related to subscales were reported in the Supplementary Material.

2.1.3.3 Functional MRI Paradigm

We used a passive avoidance task (S. F. White et al., 2013) to measure neural correlates of reinforcement learning. Each trial started with a presentation (1500 ms)

of one of the four colored shapes (Figure S2). During this period, participants had to decide whether to respond or not to a shape. A randomly jittered fixation cross (0-4000 ms) followed the presentation of the shapes. If participants responded, they received one of the four outcomes: winning 1 €, winning 5 €, losing 1 €, or losing 5 €. Each shape could engender each of these outcomes. However, the feedback was probabilistic. That is, one shape most likely resulted in a high reward, one in low reward, one in low punishment, and one in high punishment (Figure S5). If participants did not respond, they received no feedback. Participants completed 112 trials over two runs.

2.1.3.4 MRI Data Acquisition and Preprocessing

The functional and structural images were acquired on a Siemens Magnetom Prisma Fit (Siemens, Erlangen, Germany) 3T MRI scanner. During the fMRI task, 175 volumes were obtained for each run using a gradient echo-planar sequence sensitive to BOLD contrast (36 slices, TE= 35 ms, TR = 2100 ms, voxel size = 3×3×3 mm). Functional data was preprocessed using SPM 12 applying standard preprocessing steps (Supplementary Material S4).

2.1.3.5 Computational Modelling

To understand the computational mechanisms underlying participants' decision-making in the passive avoidance task, we fit the data with six reinforcement learning model families. Supplementary Material S5 provides a full description of each model family, as well as details on our model fitting and model selection procedures and the results of a parameter recovery analysis. In brief, the six model families used different variants of a Rescorla-Wagner delta learning rule and softmax choice rule to explain the trial-wise decision to either respond to a stimulus or refrain from responding. For a given trial t, the expected value of responding to a stimulus, $\mathrm{EV}_{(t)}^{\mathrm{hit}}$, is defined as follows:

$$\mathrm{EV}_{(t+1)}^{\mathrm{hit}} = \mathrm{EV}_{(t)}^{\mathrm{hit}} + \alpha \times \mathrm{PE}_{(t)} \quad (1)$$

$$\mathrm{PE}_{(t)} = \mathrm{FB}_{(t)} - \mathrm{EV}_{(t)}^{\mathrm{hit}} \quad (2)$$

Here, $\mathrm{PE}_{(t)}$ is the prediction error, which represents the discrepancy between the expected value of responding $\mathrm{EV}_{(t)}^{\mathrm{hit}}$ and the observed feedback $\mathrm{FB}_{(t)}$, and α is the learning rate parameter, which determines to what extent the prediction error is used to update the expected value. Note that the expected value of not responding to a stimulus is assumed to be fixed at $\mathrm{EV}^{\mathrm{miss}} = 0$. Thus, we henceforth use 'expected value' (EV) to refer to the expected value of responding, $\mathrm{EV}^{\mathrm{hit}}$.

Expected values were translated into action probabilities using the softmax choice rule:

$$P_{(t)}^{\mathrm{hit}} = 1 - P_{(t)}^{\mathrm{miss}} = \left(1 + \exp\left(-\beta \times \mathrm{EV}_{(t)}\right)\right)^{-1} \quad (3)$$

where β is the inverse temperature parameter, which determines the degree of randomness in action selection. The resulting trial-wise action probabilities were then used to explain each participant's observed response data.

We fit each model variant to the data using maximum likelihood estimation on a participant-by-participant basis. We then computed the Akaike information criterion (AIC) and Bayesian information criterion (BIC) for each model fit, and selected the model variant with the lowest mean AIC and BIC values as the best-fitting model (Table S4). For the selected model variant, we used each participant's set of best-fitting parameter values to extract the EV and PE time series, to be used for the fMRI analyses. Additionally, we checked if the identified adversity factors were related to task performance (omission and commission errors) and model fit measures (subject-specific model parameter estimates and AIC and BIC values). The correlation between

observed behavior (hit rate) and model-predicted behavior (hit probability) was also assessed to gauge the model's predictive validity relative to actual participant choices.

2.1.3.6 fMRI Data Analysis

At the first level, we added two onset regressors (cue and feedback phases) and their parametric modulators (EV and PE, respectively), which were convolved with the hemodynamic response using generalized linear modelling implemented in SPM 12. Six motion parameters were included as covariates of no interest to reduce the motion-related artefacts. At the second level, we performed a one-sample t-test to identify neural correlates of EV and PE signaling.

To investigate the associations between three adversity factors and EV/PE signaling, we conducted multiple regression analyses using preselected eight regions of interest (ROI): bilateral striatum (putamen, nucleus accumbens (NAcc), caudate), vmPFC, and pregenual ACC (pgACC). The regression model included an adversity measure, sex, and current psychopathology as predictors and mean activation extracted from ROIs as an outcome measure (see Supplementary Material S6 for details). All results were corrected for multiple comparisons ($p < 0.05/8$ ROIs=0.00625). To identify the contribution of specific adversity variables, we repeated the same regression analysis for each adversity measure separately. Results not surviving Bonferroni correction are reported in Supplementary Material S10.

2.1.3.7 Developmental and Contextual Analyses

2.1.3.7.1 Timing Effect of Adversities

Recently, more attention has been allocated to sensitive period for neural systems, which represents a time window of increased vulnerability to stress (Goff & Tottenham, 2015). To explore the existence of a sensitivity period in which stress exerts enduring effects on reward-related brain activity, we conducted several multiple regression

analyses using prospectively collected psychosocial adversity measures: Family adversity (T1-T5) and stressful life events (T1-T11). Due to the high number of tests and correlative nature, the findings should be considered preliminary.

2.1.3.7.2 Mediation Analysis

We performed mediation analysis using nonparametric bootstraping test implemented in R package *mediation* (https://cran.r-project.org/web/packages/mediation/) with 5000 simulations (confidence interval 95%) to see whether the association between the third adversity factor and general psychopathology symptoms was mediated by EV signaling in the striatum and pgACC. All mediation models were controlled for sex.

2.1.3.7.3 *EV Signaling and Withdrawn Symptoms throughout the COVID-19 Pandemic*

In light of findings suggesting motivational deficits in individuals exposed to adverse experiences, such as anhedonia (Souther et al., 2022), we sought to explore this further during the unique circumstances of the COVID-19 pandemic, which created a natural experiment to examine how neural alterations, particularly those related to adversity, might interact with environmental stressors to impact mental health. Hence, we examined whether lower EV signaling is a potential correlate of motivational deficits during the COVID-19 pandemic, by using the ASR withdrawn subscale, which assesses social aspects of anhedonia (e.g., social withdrawal, diminished pleasure, and lack of relationships). The timing of our COVID-19 assessments—April 2020 (n=112), June 2020 (n=108), November 2020 (n=99), and May 2021 (n=80)—allowed us to capture the evolving impact of the pandemic. We employed regression analyses utilizing a zero-inflated Poisson model to take into account excess zeros in withdrawn symptoms. All regression models were controlled for sex. P value was set to 0.05 (FDR-corrected) (see Supplementary Material S11 for details).

2.1.3.7.4 *Sensitivity Analyses*

We ensured the robustness of our results by additionally checking that adversity-related alterations do not reflect decreased general cognitive ability, are not driven by participants with current psychopathology, and checked for interaction with sex (Wellman et al., 2018). In addition, we ensured that our results on maternal sensitivity were not related to infant responsiveness (Holz et al., 2021). See Supplementary Material S12 for methods and results.

2.1.4 Results

2.1.4.1 Behavioral Results

2.1.4.1.1 Lifespan Adversity and Psychopathology

Principal component analysis identified three adversity factors. The first factor was strongly informed by *psychosocial adversities* (stressful life events, family adversity, and childhood trauma questionnaire) and *prenatal maternal smoking*. The second factor was strongly related to *perinatal adversities* (obstetric adversity and maternal stress during pregnancy). The adversity factor mostly reflected *lower maternal sensitivity during infancy* and psychosocial adversities to a lesser extent (Table S5).

The first adversity factor was associated with higher internalizing (r=0.39, FDR-p<0.001) and externalizing (r=0.35, FDR-p<0.001) symptoms. Similarly, the third adversity factor was associated with higher internalizing (r=0.16, FDR-p = 0.04) and externalizing (r=0.19, FDR-p = 0.03) problems. The second adversity factor was not related to psychopathology. The correlations between adversity measures and specific psychopathology measures can be found in Table S6.

2.1.4.1.2 Lifespan Adversity and Task Performance

We did not identify any significant correlation between adversity factors and commission errors, subject-specific model parameters, AIC, or BIC. However, we found that individuals with higher scores in the second adversity factor had higher omission errors at run 2 (r=0.17, p=0.035). This suggests potential attentional or learning challenges in these individuals (Laucht et al., 2000). Moreover, while the computational model proved to be predictive of choice behavior across the sample (average r=0.67, t(155)=43.81, p <0.001), its predictive power was inversely related to scores on the first adversity factor (r=-0.20, p=0.011). This finding indicates that while our model was robust overall, its ability to predict individual choices was somewhat

compromised in individuals with higher adversity related to early psychosocial stress and prenatal factors.

2.1.4.2 fMRI Results

2.1.4.2.1 Task Effect

A one-sample t-test was performed to identify brain regions involving EV and PE signaling. We found robust activation in key brain regions such as striatum and medial prefrontal cortex during EV and PE signaling (Figure 2; $p < 0.05$, whole-brain FWE-corrected), which was compatible with a previous meta-analysis on neural correlates of reinforcement learning (Chase et al., 2015). Detailed list of brain regions can be found in the Supplementary Material S9 (Table S8-S11).

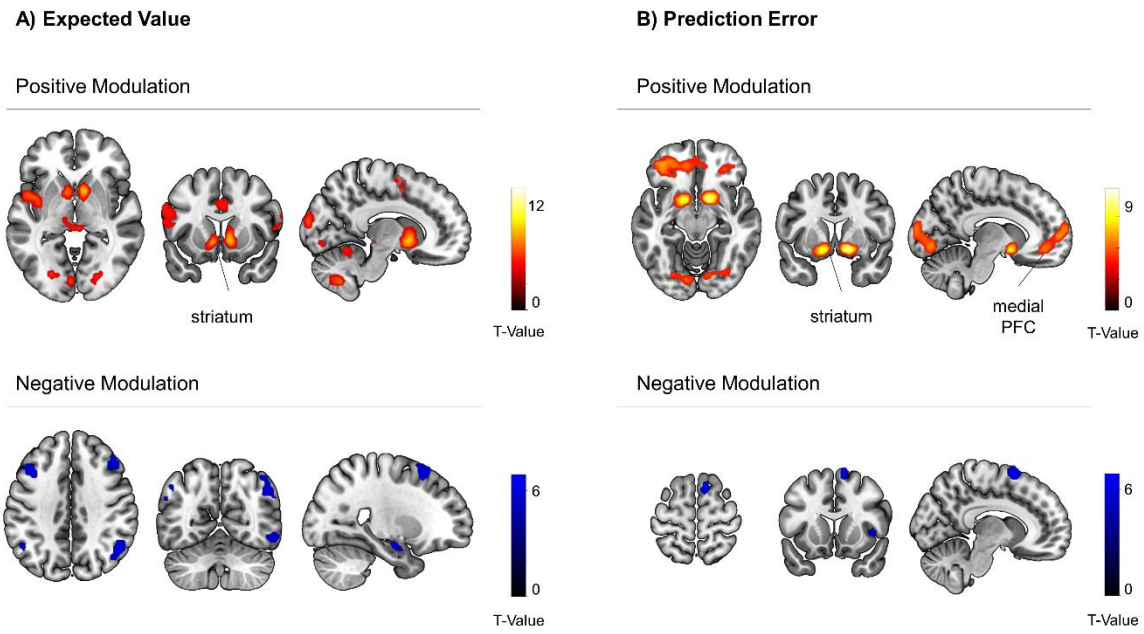

Figure 2. Expected value and prediction error signaling in the brain (p <0.05, whole-brain FWE corrected).

2.1.4.2.2 Adversity Effect

2.1.4.2.2.1 Multivariate Effects. We did not find any significant neural alteration related to the first and second adversity factors. Lower maternal sensitivity as captured by

factor 3 was associated with lower EV encoding in right striatum, specifically in the right NAcc (β=-0.23, p =0.003) and right putamen (β=-0.23, p =0.004), and pgACC (β=-0.22, p =0.006) (Figure 3). We also found lower EV signaling in right caudate, left NAcc, and vmPFC, however, these effects did not survive correction for multiple comparisons (Supplementary Material S10). Additionally, our results did not reveal any significant PE signaling alteration for any adversity factor.

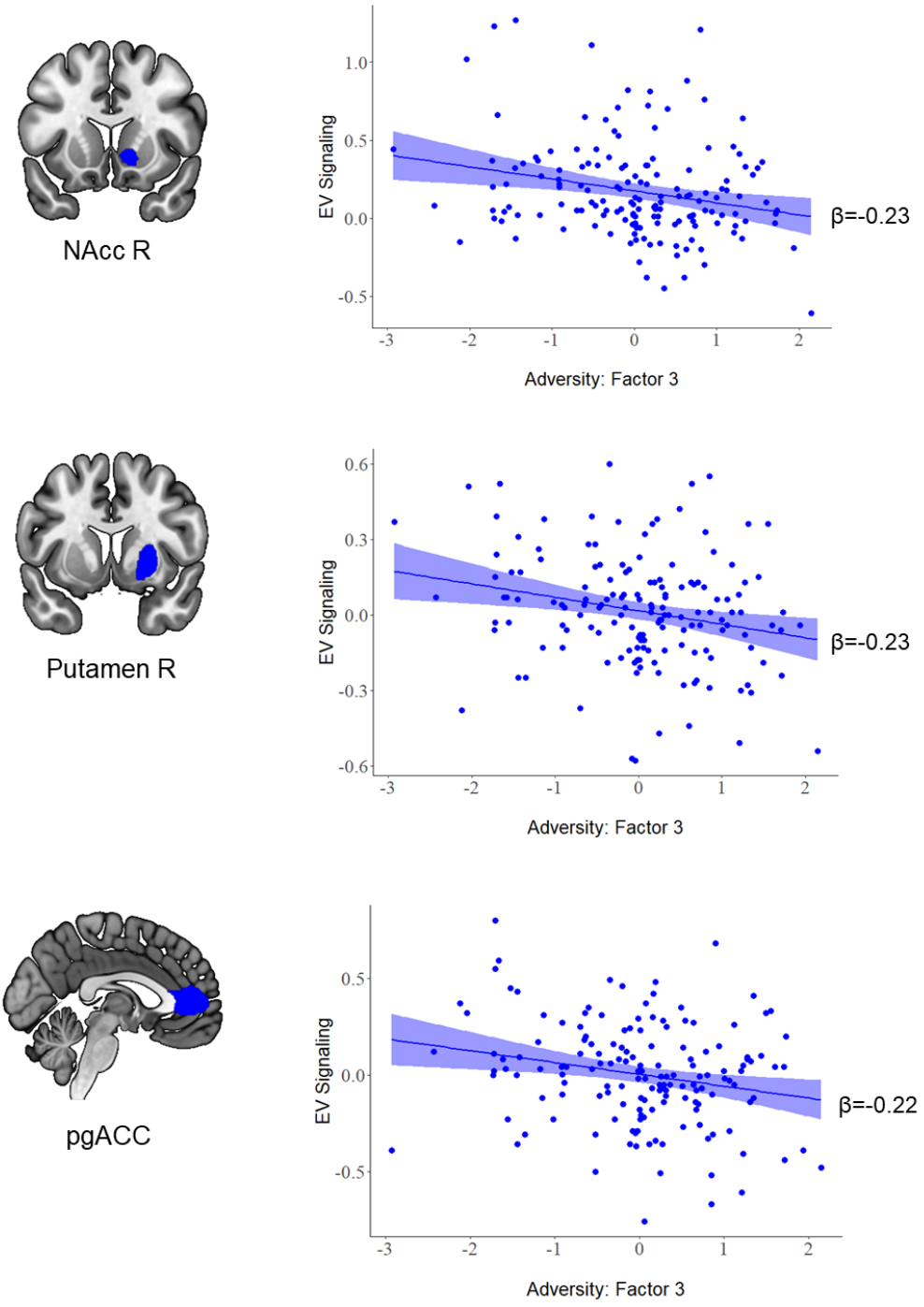

Figure 3. Associations between expected value signaling and the third adversity factor. Abbreviations: EV, expected value; NAcc, nucleus accumbens, pgACC, pregenual anterior cingulate cortex.

2.1.4.2.2.2 Specific Adversity Effects. Higher maternal stimulation was associated with higher EV encoding in right putamen (β=-0.22, p=0.006) and pgACC (β=-0.24, p =

0.002) (Figure 4). In other words, individuals who experienced lower maternal stimulation early in life had lower EV signaling in these regions. Similar effects were also found in vmPFC and right NAcc but did not survive the correction (Supplementary Material S10). No other adversity showed significant associations.

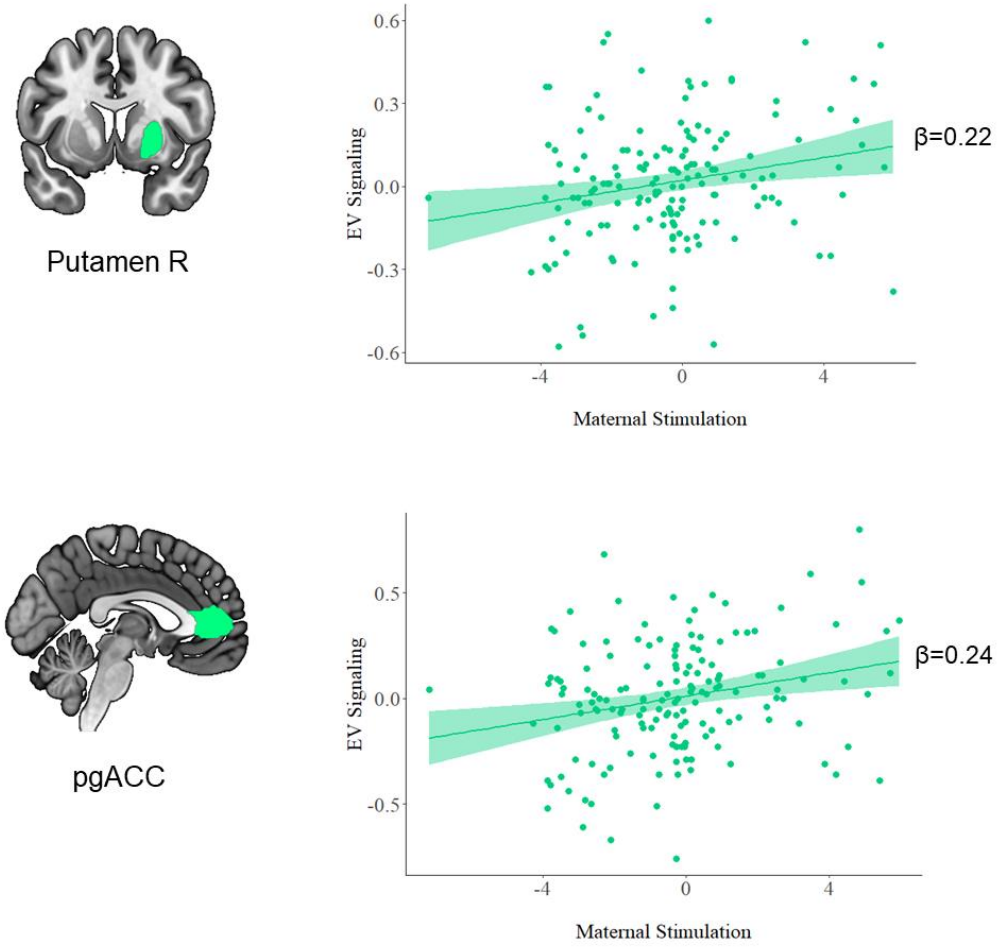

Figure 4. Associations between expected value signaling and maternal stimulation.

2.1.4.2.3 Developmental and Contextual Analyses

2.1.4.2.3.1 *Timing Effect of Adversities.* Although we found a negative association between EV signaling in the striatum and family adversity at the age of 2 and 4.5 years, these results did not survive Bonferroni correction (Supplementary Material S10). We did not find any significant association between time-specific life events measures and EV/PE signaling.

2.1.4.2.3.2 *Mediation Analysis.* The third adversity factor predicted higher scores in internalizing and externalizing problems. EV signaling in the right NAcc fully mediated the relationship between the third adversity factor and internalizing symptoms (a*b=0.37, CI= [0.04 0.79], p=0.021) (Figure 5). Mediation effect was at trend level for externalizing symptoms (a*b=0.21, CI= [-0.005, 0.50], p=0.058). No significant mediation effects were observed in other brain regions or for specific psychopathology subscales.

Having identified the mediator role of the NAcc in the association between the third adversity factor and internalizing symptoms, we further conducted a specificity analysis to see if the NAcc can also mediate the relationship between this adversity dimension and withdrawn symptoms at T11. The examination of this relationship is particularly compelling, given that withdrawn symptoms are characterized by a diminished engagement in social interactions and a reduced interest in typically rewarding activities, thereby reflecting anhedonic behavior, a condition associated with impairments in reward processing (Kangas et al., 2022). Our results revealed that the right NAcc fully mediated the relationship between the third adversity factor and withdrawn symptoms at T11 (a*b=0.12, CI= [0.02 0.25], p=0.012) (See Figure 5B).

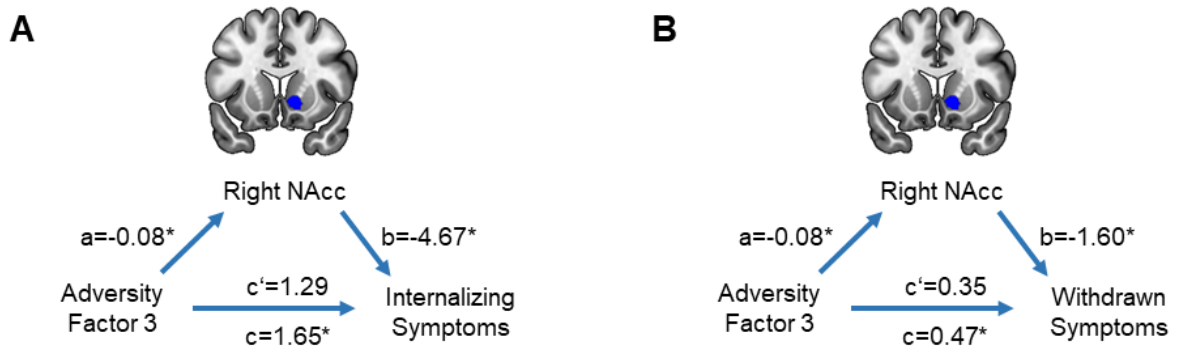

Figure 5. Mediation analysis for internalizing symptoms (A) and withdrawn symptoms (B) . The models included expected value signaling in the right nucleus accumbens as

a mediator (M) to explain the impact of adversity (X) on psychopathology symptoms (Y). Significant paths are shown with asterisk.

2.1.4.2.3.3 *EV Signaling and Withdrawn Symptoms throughout the COVID-19 pandemic.* Lower EV signaling in the right NAcc predicted withdrawn symptoms throughout the pandemic, starting from the second pandemic assessment onward (COVID-II: β=-2.70, FDR-p=0.014; COVID-III: β=-2.20, FDR-p=0.038; COVID-IV: β=-2.70, FDR-p=0.014) (Figure 6). Sex did not predict withdrawn symptoms during the pandemic.

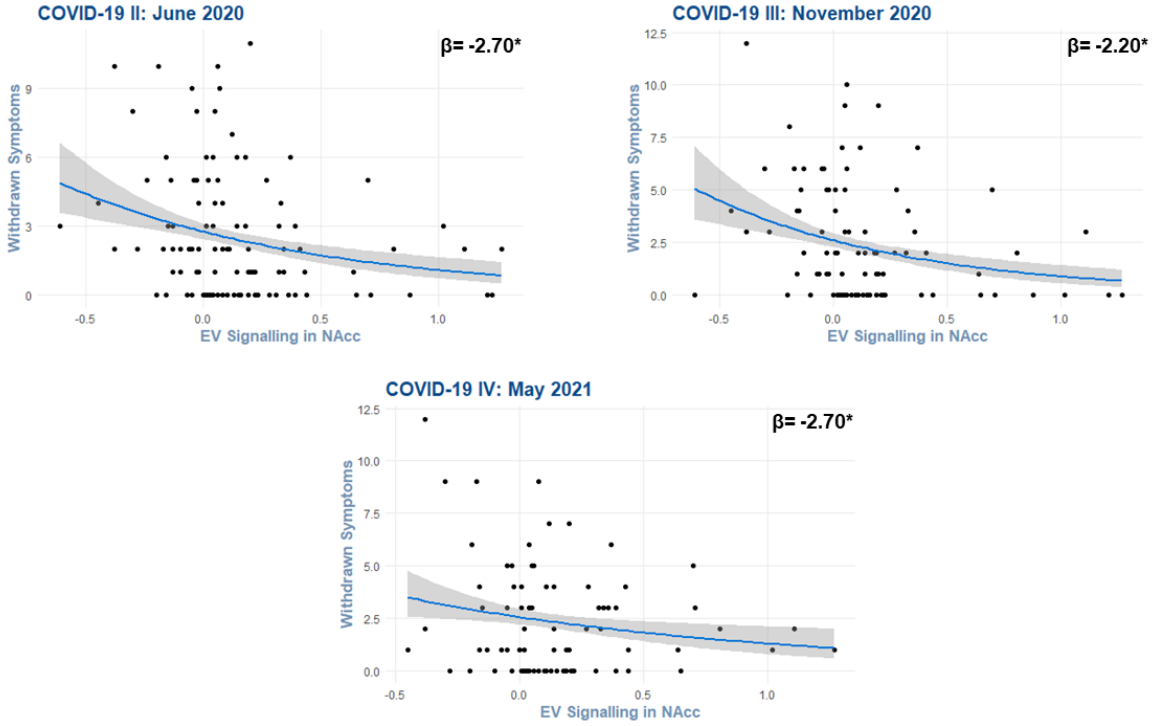

Figure 6. Associations between expected value signaling in the right nucleus accumbens and withdrawn symptoms throughout the COVID-19 pandemic .* FDR-p < 0.05.

2.1.5 Discussion

Capitalizing on data from a birth cohort, we investigated the specific and combined effect of lifespan adversities on EV and PE encoding. Our findings showed that an adversity factor primarily characterized by lower maternal sensitivity along with psychosocial adversity was associated with lower EV signaling in the right NAcc, right putamen, and pgACC. EV signaling in the right NAcc further mediated the relationship between adversity and psychopathology and predicted withdrawn symptoms during the COVID-19 pandemic. These results critically extend previous reports (Cisler et al., 2019; Gerin et al., 2017; Palacios-Barrios et al., 2021) by incorporating multiple risk factors with different developmental time windows, and offering compelling evidence for enduring neurobiological and psychopathological associations.

Our principal component analyses revealed three adversity factors, which are distinct in nature and cover different developmental time windows. The first adversity factor informed by postnatal psychosocial adversity and prenatal maternal smoking was robustly associated with higher psychopathology, in all psychopathology dimensions tested (Table S6). This underscores the pervasive impact of a combination of prenatal and postnatal adversities on adult mental health. The third adversity factor, representing lower maternal sensitivity and to a lesser extent psychosocial adversity, was also related to psychopathology but to a smaller extent (Table S6), which highlights the critical role of early maternal interactions in shaping future psychological outcomes. In contrast, the second adversity factor characterized by perinatal adversities was not linked to psychopathology, suggesting that their impact may manifest differently or may be moderated by other postnatal factors.

Higher scores in the third adversity factor were associated with lower EV signaling in the putamen, NAcc, and pgACC. As expected, we found similar neural

correlates of lower maternal stimulation, which was the major contributor for the third adversity factor. These results are in line with several previous studies reporting functional (Birn et al., 2017; Boecker et al., 2014; Casement et al., 2013; Hendrikse et al., 2022; Holz et al., 2017; Mehta et al., 2010), structural (Gold et al., 2016; Price et al., 2021) and white matter tract (DeRosse et al., 2020; Kennedy et al., 2021) abnormalities in the striatum and prefrontal cortex in individuals exposed to adversity. However, it is important to note that the adversity-related neural alterations we observed were specifically evident during EV signaling. Given that lower EV signaling may reflect diminished reward anticipation, these findings resonate with our earlier report of reduced striatal responses during reward anticipation in individuals with higher adversity, using data from the same cohort at the 25-year assessment (Boecker et al., 2014), but also provide a more nuanced understanding by specifically pinpointing the computational mechanisms likely influenced by early adversities. This consistency in findings across different time points reinforces the notion that adversity has a lasting impact on neural mechanisms underlying reward processing.

Similar to our main findings, a previous study reported associative learning deficits in institutionalized children, suggesting a disruptive effect of psychosocial deprivation (e.g., caregiver absence) on learning. These findings underscore the critical role of early sensory input and stable caregiver experiences on reward learning, which are essential for learning, exploration and normative brain development (Fareri & Tottenham, 2016; Gee et al., 2018; Novick et al., 2018). Inconsistent caregiver behavior can create an unstable environment where the rewards are sparse and random, and thus impair the utilization of environmental information to optimize the behavior (Novick et al., 2018). In contrast, consistent and good quality maternal care can buffer negative outcomes of adverse experiences on reward processing, as we

previously showed that higher maternal stimulation was linked to increased striatum activation during reward anticipation in young adults with parental psychopathology (Holz et al., 2018).

Moreover, we showed that EV signaling in the right NAcc mediated the relationship between the third adversity factor and internalizing symptoms. The NAcc plays a key role in reward processing and motivational behavior (Day & Carelli, 2007). Furthermore, several previous studies identified neural EV/PE abnormalities in the striatum for several psychiatric conditions including depression (Gradin et al., 2011), substance abuse (S. F. White, Tyler, Botkin, et al., 2016), anxiety (S. F. White et al., 2017), and conduct disorder (Zhang et al., 2021), potentially indicating a transdiagnostic mechanism. Taken together, these results suggest that disruptions in striatal EV signaling might increase the risk of developing psychopathology in individuals exposed to adversities by affecting neural correlates of decision-making processes.

Disrupted EV signaling in individuals exposed to adversities may be linked to impairments in several important skills such as approach behavior and risk/benefit assessment (Birn et al., 2017; Holz et al., 2017). These cognitive skills are particularly crucial for adapting to rapidly evolving situations that demand flexibility, such as those encountered during the COVID-19 pandemic. In line with this reasoning, we provided evidence for lower EV signaling in the NAcc being associated with higher withdrawn symptoms during the pandemic. The associations suggest that EV signaling relates to social withdrawn under pandemic-related stress, which aligns with existing literature that establishes a connection between reinforcement abnormalities, adversity, and anhedonia (Bolton et al., 2018; Kangas et al., 2022; Palacios-Barrios et al., 2021; Souther et al., 2022). Such findings illuminate that individuals with diminished reward

processing capacity in the NAcc—a central hub for motivation and pleasure—face substantial challenges in engaging with and finding enjoyment in social interactions and activities potentially heightening the risk for developing psychopathologies. However, it is crucial to emphasize that these associations, while statistically significant, do not imply causality.

Lastly, several studies suggested that stressors occurring in early life are more likely to affect reward circuitry (Birnie et al., 2020; Boecker et al., 2014; Novick et al., 2018). Indeed, a previous study found that the striatum was sensitive to maltreatment that occurred between the ages of 0-4 years (Takiguchi et al., 2015). Although we found some evidence for the vulnerability of the striatum to early life stress (Supplementary Material S10, there results did not survive the statistical correction for multiple comparisons. Therefore, more research is needed to make inferences about the sensitivity period for the reward network.

2.1.5.1 Limitations

The current study has several limitations. First, we did not investigate the differential neural responses to reward and punishment prediction errors to increase power in the statistical analysis. However, several studies suggest that reward and loss networks are similar (Oldham et al., 2018; Tom et al., 2007). Second, our sample predominantly consisted of participants without clinical diagnoses, which limits the generalizability of our findings to populations with higher levels of psychopathology. Although we observe neural alterations that could potentially indicate vulnerability, the limited variation in psychopathological symptoms warrants further validation in clinical samples. Third, we assessed adversity measures mostly early in development but measured brain responses in adulthood only. Although a longitudinal design such as in this study offers valuable insights in terms of prospective associations, it does not provide causal

inferences, for which longitudinal neuroimaging would have been necessary. Fourth, some adversity measures (e.g., childhood trauma, family adversity) reflect the sum of several different adverse experiences. While this aggregated approach provides a useful framework for a broad assessment of adversity, it inherently limits the specificity of our results with respect to these particular adversities.

2.1.5.2 Conclusions

In conclusion, we showed that the adversity factor mainly informed by lower maternal sensitivity but also postnatal psychosocial adversities was linked to altered neural EV signaling in the core reward network in adulthood. Furthermore, neural alterations in NAcc mediated the relationship between adversity and internalizing psychopathology and predicted withdrawn symptoms during the COVID-19 pandemic. Highlighting the potential clinical significance of these neural alterations, our findings underscore the importance of early preventive and intervention strategies. Strategies targeting the developmental stages crucial for shaping the brain's reward processing mechanisms could mitigate the long-term psychopathological risks associated with early adverse experiences.

2.2 Study II: Lifespan adversities affect neural correlates of behavioral inhibition in adults

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2.2.1 Abstract

Growing evidence suggests that adverse experiences have long-term effects on executive functioning and underlying neural circuits. Previous work has identified functional abnormalities during inhibitory control in frontal brain regions in individuals exposed to adversities. However, these findings were mostly limited to specific adversity types such as maltreatment and prenatal substance abuse. We used data from a longitudinal birth cohort study (n=121, 70 females) to investigate the association between adversities and brain responses during inhibitory control. At the age of 33 years, all participants completed a stop-signal task during fMRI and an Adult Self-Report scale. We collected seven prenatal and postnatal adversity measures across development and performed a principal component analysis to capture common variations across those adversities, which resulted in a three-factor solution. Multiple regression analysis was performed to identify links between adversities and brain responses during inhibitory control using the identified adversity factors to show the common effect and single adversity measures to show the specific contribution of each adversity. To find neural correlates of current psychopathology during inhibitory control, we performed additional regression analyses using Adult Self-Report subscales. The first adversity factor reflecting prenatal maternal smoking and postnatal psychosocial adversities was related to higher activation during inhibitory control in bilateral inferior frontal gyri, insula, anterior cingulate cortex, and middle temporal gyri. Similar results were found for the specific contribution of the adversities linked to the first adversity factor. In contrast, we did not identify any significant association between brain responses during inhibitory control and the second adversity factor reflecting prenatal maternal stress and obstetric risk or the third adversity factor reflecting lower maternal sensitivity. Higher current depressive symptoms were associated with higher

activation in the bilateral insula and anterior cingulate cortex during inhibitory control. Our findings extended previous work and showed that early adverse experiences have a long-term effect on the neural circuitry of inhibitory control in adulthood. Furthermore, the overlap between neural correlates of adversity and depressive symptomatology suggests that adverse experiences might increase vulnerability via neural alterations, which needs to be investigated by future longitudinal research.

2.2.2 Introduction

Executive functions (EF) are essential cognitive skills for adaptation, social functioning, and goal-directed behavior (Zelazo, 2020). Deficits in EF have been documented in several psychiatric disorders, indicating that EF impairments may be a transdiagnostic correlate for psychopathology (Snyder et al., 2015, 2019). Previous findings showed that exposure to adverse childhood experiences is associated with both EF difficulties (Lund et al., 2020, 2022) and poor mental health outcomes (K. Hughes et al., 2017; McKay et al., 2021), which lead to a developmental model suggesting that childhood adversities and other sources of stress may disrupt the neural systems supporting EF and thereby increase the risk of developing psychopathology (Zelazo, 2020). However, due to scarcity of longitudinal neuroimaging research, temporal dynamics of these relations have not been elucidated yet.

Inhibitory control is a core component of EF and a fundamental aspect of self-regulation, which requires suppressing a behavior or emotion when responding is no longer necessary or inappropriate (Diamond, 2013). At the neural level, successful behavioral inhibition requires the involvement of several frontal regions, such as the inferior frontal gyrus, and the pre-supplementary motor area (Aron & Poldrack, 2006; Cai et al., 2014; Korucuoglu et al., 2021; Rubia et al., 2003; Steele et al., 2013), whereas unsuccessful inhibition leads to enhanced activity in the dorsal anterior cingulate cortex (Duann et al., 2009; Korucuoglu et al., 2021; Rubia et al., 2003), more likely reflecting error processing (Dali et al., 2023). Several studies found that individuals exposed to adverse childhood experiences showed altered frontal activation in these regions during inhibitory control tasks (Bruce et al., 2013; Demers et al., 2022; Holz et al., 2014; Lees et al., 2020; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015). However, the direction of the alterations changed based on the

specific experimental paradigm used. Higher adversity was associated with higher activation in frontal regions in studies using the stop-signal task (Lees et al., 2020; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015), whereas the reverse pattern was identified in the studies using the Go/No Go task (Bruce et al., 2013; Demers et al., 2022; Holz et al., 2014). Although both Go/No Go and stop-signal tasks were commonly used in the context of response inhibition and require suppression of a dominant response, they involve distinct mechanisms, namely action restraint and action cancellation respectively (Raud et al., 2020), which might explain conflicting directional associations found in previous literature.

Similar neural alterations, as found for adversities, were also identified in the context of psychopathology. Previous studies have reported abnormal prefrontal cortex activation during inhibitory control in several clinical conditions, including depression (Malejko et al., 2021; Nixon et al., 2013), attention deficit and hyperactivity disorder (Massat et al., 2018), posttraumatic stress disorder (Aupperle et al., 2016), and eating disorder (Bartholdy et al., 2019), indicating that altered frontal activation during inhibitory control can be a neural vulnerability correlate of psychopathology. However, the direction of the alteration was not consistent across the studies.

Although previous studies provided evidence for the relationship between childhood adversities and neural correlates of inhibitory control, there are several gaps in the literature that need to be addressed. First, the previous studies examined the effect of a single adversity measure on neural inhibitory network. However, it is plausible that different adversities could have common effects in addition to distinct associations with neural systems. Moreover, different adversities tend to occur together (Holz, Berhe, et al., 2023). Focusing on a single adversity measure may not only reflect the effect of specific adversity but also the effect of co-occurring adversities.

Therefore, investigating shared effects as well as specific effects of diverse experiences will bring new insights. Second, most of the studies limited their findings to adolescent samples, except two previous studies conducted in adults using the Go/No Go paradigm (Demers et al., 2022; Holz et al., 2014). Therefore, complimentary research is necessary to show if the long-term effect of adversities on neural inhibitory network is identifiable in other inhibitory control contexts. Third, most of the previous studies utilized liberal thresholds for reporting neuroimaging results (Bruce et al., 2013; Demers et al., 2022; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015), and some additionally investigated small sample sizes (Bruce et al., 2013; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015).

The current study aimed to address these gaps by investigating the specific and cumulative effects of several lifespan adversities on neural responses during inhibitory control using the stop-signal task in a cohort of adults followed since birth. We collected several risk measures across development, which included prenatal factors such as maternal stress and maternal smoking, perinatal factors such as obstetric adversity, and postnatal factors such as low maternal care, family adversity, stressful life events, and self-reported childhood trauma. We hypothesized that adversities across development would be associated with increased functional activation in several frontal regions, including the inferior frontal gyrus (IFG), pre-supplementary motor area (pre-SMA), and dorsal anterior cingulate cortex (dACC) during inhibitory control. Furthermore, altered frontal activation would be associated with lower inhibition success and higher psychopathology symptoms in adulthood.

2.2.3 Methods and Materials

2.2.3.1 Participants

The current study was conducted within the framework of Mannheim Study of Children at Risk. The initial sample included 384 infants recruited from two obstetric and six children´s hospitals in the Rhine-Neckar region of Germany between 1986 and 1988. Participants were followed from their birth up to around the age of 33 years (age range: 31.7- 34.5 years) across 11 assessment waves. At the last assessment wave (T11), 256 participants (67%) agreed to participate in the study and completed several psychological measurements. fMRI data for the stop-signal task was available for 170 participants. We used an extensive quality check procedure covering fMRI data quality (e.g., head motion, signal loss etc.), and task performance metrics based on a consensus guide for the stop-signal task (Verbruggen et al., 2019) (See Supplementary Material S1 for a detailed description of exclusion criteria). Four participants were excluded due to low fMRI data quality. An additional 45 participants were excluded due to poor task performance during go trials (correct go < 80%), having inhibition success lower than 25% or greater than 75%, and having greater mean reaction time for unsuccessful stop trials than go trials. The final sample included 121 participants (Table 2). Of 121 participants, 16 participants fulfilled the criteria for a current psychopathology including major depressive disorder (n=5), anxiety disorder (n=7), alcohol and substance abuse (n=3), and schizophrenia (n=1).

Table 2. Study II sample characteristics.

	N=121
Age, M(SD)	32.2 (0.3)
Sex, N, F/M	70/51
Head Motion [a], M (SD)	0.12 (0.05)
Maternal Smoking, N, non-/moderate/heavy smoker	89/11/21
Maternal Stress, M(SD), range	2.78 (1.9), 0-8
Obstetric Adversity, N, no/moderate/high risk	41/72/8
Maternal Stimulation [b], M(SD), range	-0.27 (2.39), -7.18-5.96
CTQ total, Median(IQR), range	28 (5.5), 25-68
Family Adversity, M(SD), range	3.39 (2.45), 0-10
Stressful Life Events [c], M(SD), range	-0.56 (6.18), -11.23-22.27
ADHD, Median(IQR), range	4(6), 0-14
Antisocial Personality, Median(IQR), range	2(4), 0-11
Anxiety, Median(IQR), range	3(3), 0-9
Avoidant Personality, Median(IQR), range	2(4), 0-11
Depression, Median(IQR), range	3(5), 0-19
Somatic Problems, Median(IQR), range	1(2), 0-11

[a] Frame-wise displacement. Measurement unit is millimeters.
[b] We used reversely-coded z-transformed scores. Higher scores indicated lower maternal stimulation.
[c] We used the sum score of z-transformed total scores across the 11 assessment waves.

2.2.3.2 Psychological Measurements

2.2.3.2.1 Adversity Measurements

The Mannheim Study of Children Risk included several adversity measures across the development, which were previously associated with abnormal brain development and functioning (Entringer et al., 2015; Hart et al., 2018; Holz et al., 2014; Mueller et al., 2010; Philip, Sweet, Tyrka, Price, Bloom, et al., 2013). For the prenatal period, we included maternal stress (Zohsel et al., 2014) and maternal smoking (Holz et al., 2014), which were measured using a standardized interview during the 3-month assessment at T1. Obstetric adversity (Laucht et al., 2000) included obstetric complications as a

measure of perinatal risk. Postnatal measures included several psychosocial measures such as maternal stimulation (Holz et al., 2018) during infancy (3-month assessment), family adversity (Holz et al., 2017) from birth to up to 11 years (T5), stressful life events (Maier-Diewald et al., 1983) from birth to up to around 33 years (T11), and self-reported childhood trauma at T9 (23 years) using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994). Detailed descriptions for each adversity measure can be found in Table 3. Similar to our previous study (Holz, Zabihi, et al., 2023), we applied a principal component analysis in IBM SPSS (version 27) using the above-mentioned adversity measures to reduce the dimensionality and account for correlative nature of the adversity measures (Table S1). We identified three components with an eigenvalue > 1, which in total explained 66.8% of the variance in the data (see details in Results).

Table 3. Adversity measures.

Measurement	Measurement Time	Descriptions
Maternal Smoking	T1 (3 months)	Maternal smoking measured daily cigarette consumption of mothers (1= no, 2= up to 5 per day, 3= more than 5 per day) during pregnancy using a standardized interview.
Maternal Stress	T1 (3 months)	Maternal stress was measured using a standardized interview. Mothers answered 11 questions covering negative experiences and reversely coded positive experiences during the second and third trimesters of pregnancy (e.g., 'Did you have mood swings/ a depressed mode?').
Obstetric Adversity	T1 (3 months)	Obstetric adversity included obstetric complications (e.g., low birth weight, preterm birth, medical complications). The score ranged between 0 and 4 (0=no risk, 1-2=moderate risk, 3-4=high risk).
Maternal Stimulation	T1 (3 months)	Maternal stimulation was based on video recordings of mother-infant interactions (10 minutes) in a play and nurse setting. Trained raters evaluated mothers' attempts (vocal, facial or motor) to draw infants' attention. The scores were z-transformed and recoded such that higher scores indicated lower maternal stimulation.
Family Adversity	T1 – T5 (3 months – 11 years)	Family adversity measured the presence of 11 adverse family factors from birth to 11 years such as parental psychopathology, lower parental education, and marital discord.
Stressful Life Events	T1 – T11 (3 months – 33 years)	We measured stressful life events (e.g., presence of several life stressors in different domains such as partnership, education, work, health, and finance) across the development using an adapted version of the Munich Event List (Maier-Diewald et al., 1983). The sum of Z-transformed scores calculated for each time point (T1-T11) was used for the analyses.
Childhood Trauma	T9 (23 years)	Participants reported retrospectively the presence of traumatic childhood experiences using the German version of Childhood Trauma Questionnaire (Wingenfeld et al., 2010) covering five subscales (emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse). Total scores were used for the analyses.

2.2.3.2.2 Psychopathology

We used the Adult Self-Report (Achenbach & Rescorla, 2003) to assess current symptoms of psychopathology. The Adult Self-Report includes 126 items rated on a 3-

point Likert scale (0= ‘not true’, 1= ‘somewhat or sometimes true’, 2= ‘very true or often true’) assessing mental health problems, adaptive functioning, and substance use. As measures of psychopathology, we used the total scores of six DSM-oriented subscales, including depression, anxiety, avoidant personality, somatic problems, attention deficit and hyperactivity disorder (ADHD) and antisocial personality scales.

2.2.3.3 Experimental Paradigm

We used the stop-signal task (Rubia et al., 2003) to assess inhibitory control during fMRI (Figure S1). The task contained 160 trials (6.37 minutes), which consisted of two types of trials (go trials and stop trials). Each trial began with a fixation cross, which was followed by an arrow pointing to the left or right (go-signal). In the majority of trials (75%), participants were required to respond as quickly and accurately as possible by pressing the left or right button according to the previously shown arrow. Infrequently (25%), an arrow pointing upward (stop-signal) followed the go signal. During the stop trials, participants were asked to inhibit their response, which resulted in either successful or unsuccessful inhibition. The delay between go-signal and stop-signal started at 250 ms and increased by 50 ms if participants successfully inhibited their response (max 900 ms) or decreased by 50 ms if they failed (min 50 ms). This procedure enabled an approximately equal number of successful and unsuccessful stop trials. The inhibition success (successful stop trials / all stop trials) was on average 58.1% (SD=8.9) in the current sample.

2.2.3.4. Data Acquisition and Preprocessing

The functional and structural images were acquired on a Siemens Magnetom Prisma Fit (Siemens, Erlangen, Germany) 3T MRI scanner with a standard 32-channel head coil. During the stop-signal task, 186 volumes were obtained using a gradient echo-planar sequence sensitive to blood oxygen level-dependent (BOLD) contrast (36

slices, TE= 35 ms, TR = 2100 ms, voxel size = 3 × 3 × 3 mm). More information on the scanning parameters can be found in the Supplementary Material S4 (Table S2&S3).

Functional data was preprocessed using SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The first six volumes were discarded to allow for equilibration of the magnetic field. The preprocessing steps included slice timing correction of volumes to the middle slice, realignment to the first volume using a rigid body linear transformation, structural and functional image co-registration, segmentation, normalization to the Montreal Neurological Institute template, and smoothing using a kernel with a full-width half-maximum of 8 mm.

2.2.3.5 Generalized Linear Modelling

2.2.3.5.1 First-Level Generalized Linear Modeling

Experimental conditions (correct go trials, successful stop trials, and unsuccessful stop trials) were convolved with a canonical hemodynamic response function using SPM 12. To quantify head motion, we calculated framewise displacement based on six motion parameters (Power et al., 2014). If a participant had scans with framewise displacement greater than 0.5, we then censored those scans by creating a dummy-coded regressor (Cisler et al., 2018). Six motion parameters, the regressor representing the censored scans, and time series from white matter and cerebrospinal fluid were entered into the first-level analysis as nuisance covariates to correct for motion and physiological noise. Having performed the first-level analysis, we created two widely used t-contrasts (Lees et al., 2020; Li et al., 2019; Rubia et al., 2003) in the literature: Successful stop trials > correct go trials and successful stop trials > unsuccessful stop trials.

2.2.3.5.2 Second-Level Generalized Linear Modeling

All second-level analyses were conducted using SPM 12. We first performed a one-sample t-test to identify brain regions showing the main task effect. Results were thresholded at $p < 0.05$ (whole-brain family-wise error (FWE) corrected, cluster size > 10).

We then conducted a series of multiple regression analyses to examine the association between three adversity factors and brain responses during inhibitory control on a whole-brain level. Sex and current psychopathology were included as covariates of no interest in all analyses. The same regression analysis was performed for each adversity measure separately.

In addition, we conducted regression analyses to explore brain-behavior relationship using task performance and psychopathology measures. We calculated several task performance metrics including the percentage of successful stop trials (i.e., number of correct stop trials / all stop trials) as a measure of inhibition success and stop-signal reaction time (SSRT) (Logan et al., 2014) as a measure of inhibition speed (Mennes et al., 2012). Previous literature suggests that lower SSRT is related to higher inhibitory control (Mennes et al., 2012). Unexpectedly, lower SSRT here was associated with higher commission errors during go trials (r_s=-0.27, $p < 0.01$), indicating that the higher the inhibition speed, the higher the commission error. This could be the case because healthy adults can develop a strategy (e.g., waiting longer) to increase inhibition success. Given the high correlation between the two metrics (r=0.62, p <0.001) and conflicting results regarding the SSRT, we opted to use inhibition success as a measure of task performance since inhibition success might be a more meaningful measure than inhibition speed in real-life settings. The results for the SSRT are presented in the Supplementary Material S10.

To identify if there is an overlap between neural correlates of adversity and specific psychopathology, we first performed regression analyses using the above-mentioned six DSM-oriented Adult Self-Report subscales and then identified the regions showing both adversity and psychopathology effects by intersecting SPM whole-brain association maps.

All results were thresholded at a whole-brain level using $p < 0.001$ as a cluster-forming threshold, and the clusters with $p < 0.05$ corrected for FWE are reported in the results.

2.2.3.6 Statistical Analyses

All statistical analyses were performed in IBM SPSS version 27. The analyses encompassed demographics for sample characteristics and correlation analyses to examine association the association between adversities and psychopathology. P was set to 0.05 (two-tailed). Due to non-normally distributed data for psychopathology measures (n=6), we conducted a Spearman's correlation test and applied Bonferroni correction to correct for multiple testing problem ($p < 0.05 /6= 0.008$).

2.2.3.7 Post-hoc Analyses

We identified adversity related alterations only during successful versus unsuccessful stop trials. However, this differential contrast did not reveal whether the activation difference was arisen due to more activation or less deactivation in one condition compared to other. Therefore, we further performed one sample t-tests using contrast images for successful stop trials (versus baseline) and unsuccessful stop trials (versus baseline). We then intersected the task and adversity effect maps obtained from second-level SPM analysis to identify regions showing shared effect.

Moreover, having identified the relationship between the first adversity factor and psychopathology measures, we conducted mediation analysis to see if neural

responses mediates this relationship. For this purpose, we extracted mean activation from the clusters significantly related to adversity using the MarsBar toolbox (https://www.nitrc.org/projects/marsbar). Mediation analysis was performed using the PROCESS toolbox (Hayes, 2012) implemented in IBM SPSS version 27. In total, we tested 30 mediation models (five clusters x six psychopathology scales) using the model 4 from the PROCESS toolbox. To approximate the rigor of multiple comparisons correction, we set our confidence intervals to 99% and increased the number of bootstrap samples to 10,000. Each mediation model included mean activation from a cluster associated with adversity as a mediator (M) to explain the impact of the first adversity factor (X) on psychopathology symptoms (Y).

In the current study, we used the sum scores of two psychosocial adversity measures that were assessed at multiple time points across development, namely family adversity (presence of 11 adverse family factors up to 11 years) and stressful life events (sum scores of the life events at each assessment wave up to 33 years). However, this approach does not allow to disentangle timing effects of adversities on neural systems. Given that the literature suggests that adverse experiences may exert more detrimental effects during specific developmental windows than the others (Weiss & Wagner, 1998), we performed regression analyses using the time-specific measures for family adversity (n=5) and stressful life events (n=11) ($p < 0.001$ at whole-brain, $p < 0.05$ FWE corrected at cluster level) in a further exploratory sensitivity analysis. All analyses were controlled for sex and current psychopathology. Due to the high number of tests and correlative nature, the findings should be considered preliminary.

2.2.4 Results

2.2.4.1 Behavioral Results

The principal component analysis identified three adversity factors (Table S4). The first adversity factor was strongly informed by stressful life events, family adversity, maternal smoking, and childhood trauma questionnaire. The second adversity factor was strongly related to obstetric adversity and maternal stress. The third adversity factor mostly reflected maternal stimulation. Similar to our previous work with a larger sample (Sacu et al., 2023), we found that the first adversity factor was associated with higher scores in all psychopathology measures except for somatic problems (all $p < 0.05$, Bonferroni-corrected, Supplementary Material S6). We did not identify any association between psychopathology measures and the second and third adversity factors, although the latter association was significant in the larger sample (Sacu et al., 2023).

2.2.4.2 Task Effect

We performed a one-sample t-test to identify neural correlates of inhibitory control. The results are shown in Figure 7. During successful stop versus go trials, we found increased activation in several brain regions, including bilateral angular gyrus, middle temporal gyrus, cerebellum, precuneus, occipital regions, motor regions (precentral gyrus, postcentral gyrus, supplementary motor area), posterior insula, IFG, anterior cingulate cortex, orbitofrontal cortex, middle frontal gyrus, hippocampus, right amygdala, and left parahippocampal gyrus ($p < 0.05$, whole-brain FWE corrected; Table S5). We additionally identified decreased activation in the bilateral anterior insula extending to the posterior IFG, bilateral putamen, and left midbrain ($p < 0.05$, whole-brain FWE corrected; Table S5).

Similarly, during successful versus unsuccessful stop trials, we identified increased activation in a large cluster including bilateral occipital regions, striatum, frontal regions (middle, superior, and inferior frontal gyrus), motor regions (precentral gyrus, postcentral gyrus, SMA), middle temporal gyrus, superior temporal gyrus, precuneus, angular gyrus, amygdala, hippocampus, and left cerebellum ($p < 0.05$, whole-brain FWE corrected; Table S5). In addition, we found decreased activation bilaterally in the anterior insula, orbitofrontal cortex, superior medial prefrontal cortex, dACC, and pre-SMA ($p < 0.05$, whole-brain FWE corrected; Table S5).

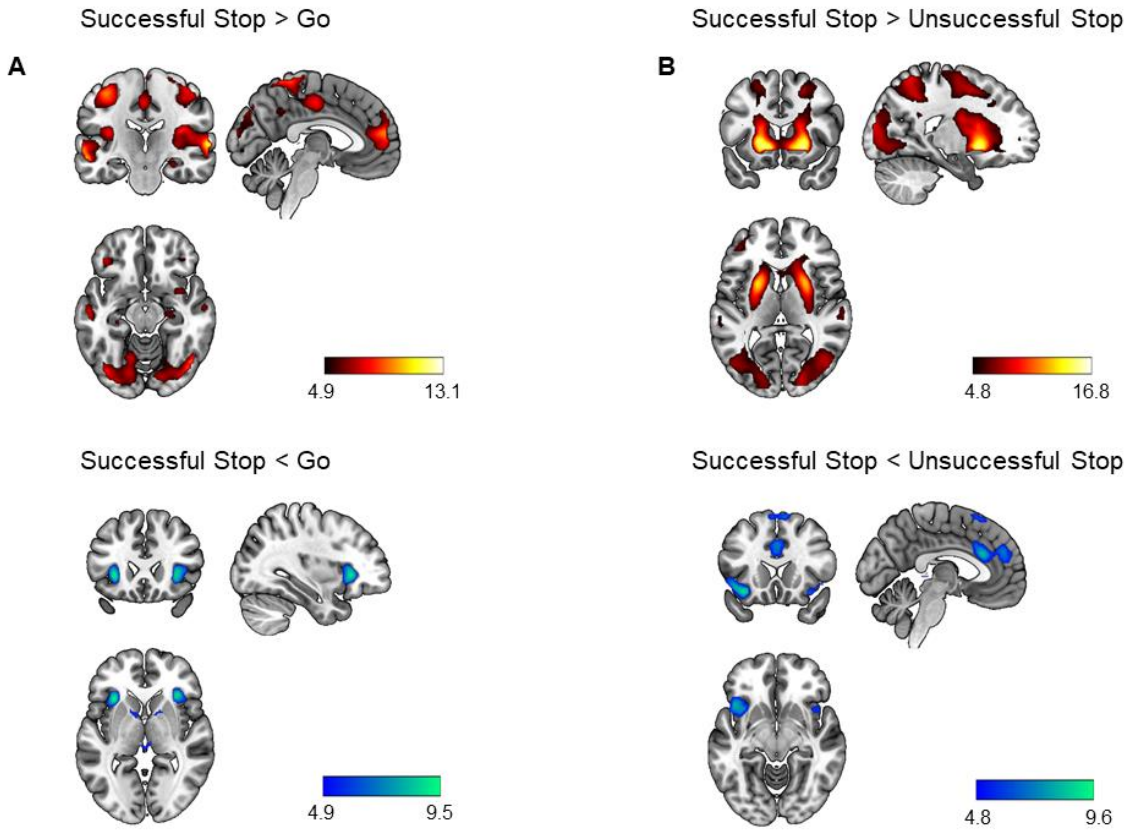

Figure 7. Brain regions showing task effect during the stop signal task ($p < 0.05$, whole-brain FWE corrected). Successful stop versus go trials (A) and successful stop versus unsuccessful stop trials (B) contrasts were chosen to identify neural correlates of inhibitory control. The hot colors represent increased activation, whereas the cold

colors represent decreased activation for the contrast of interest. Results were mapped on the brain surface using MRIcroGL (https://www.nitrc.org/projects/mricrogl).

2.2.4.3 Adversity Effect

1.2.4.3.1 Adversity Factors

We identified five clusters showing positive correlation with the first adversity factor representing postnatal psychosocial adversities and prenatal maternal smoking (all $p < 0.05$, cluster-level FWE corrected; Figure 8). These clusters included left middle temporal gyrus (MTG) ($t=5.25$, $k=95$, $p < 0.001$), right MTG ($t=4.34$, $k=64$, $p=0.04$), left insula extending to left IFG and left orbitofrontal cortex ($t=5.10$, $k=259$, $p < 0.001$), right insula extending to right IFG and right superior temporal gyrus (STG) ($t=4.78$, $k=306$, $p < 0.001$), and superior medial prefrontal cortex (mPFC) extending to dACC and middle cingulum ($t=5.19$, $k=277$, $p < 0.001$). Higher scores in the first adversity factor were associated higher activation in these regions during the successful versus unsuccessful stop trials.

We did not identify any cluster exhibiting correlation with the second and third adversity factors. Additionally, we did not identify any adversity-related alteration in brain activation for the successful stop versus go trials contrast.

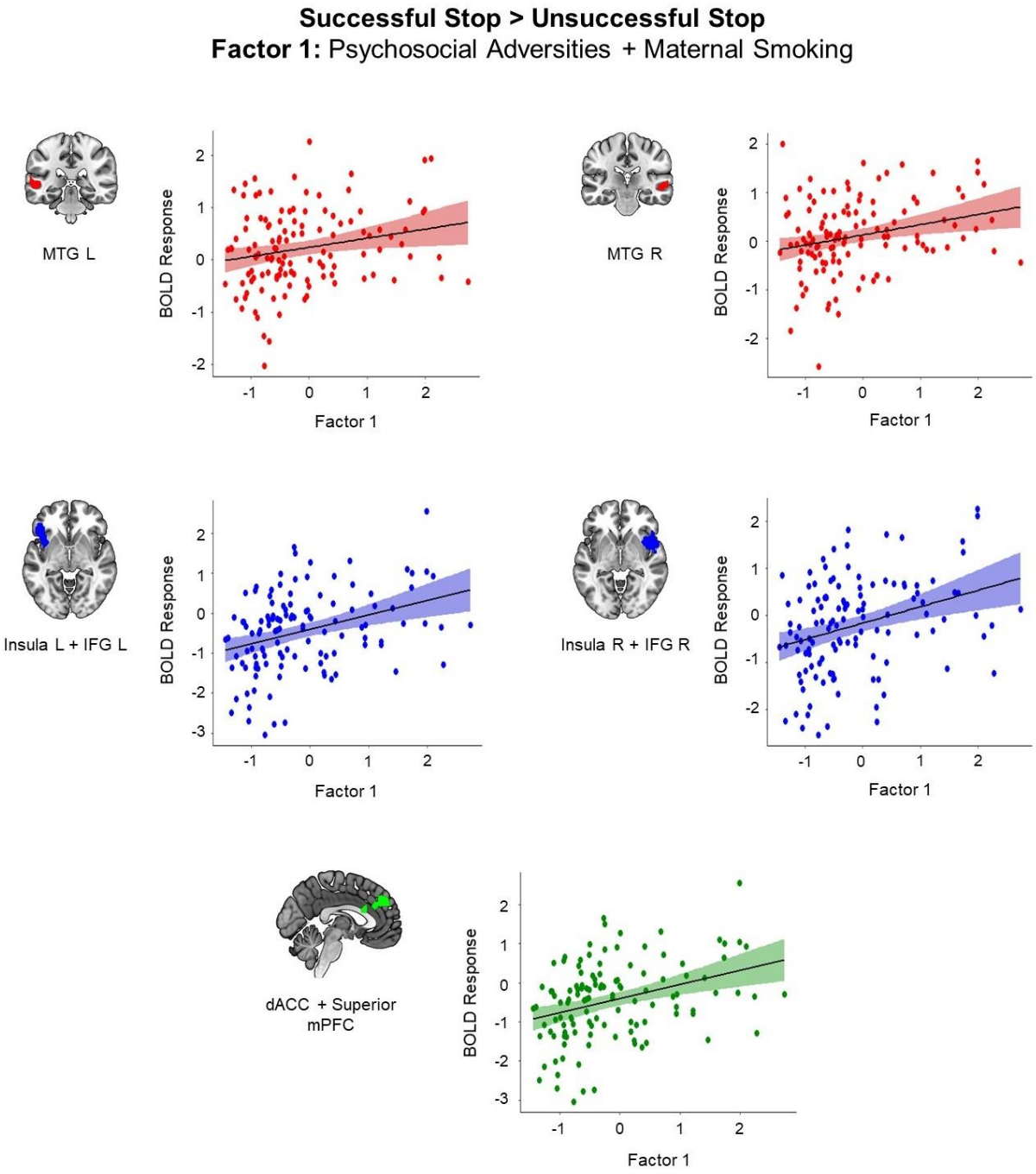

Figure 8. Brain regions showing positive associations with the first adversity factor during the successful versus unsuccessful stop trials (all $p < 0.05$, cluster-level FWE corrected). Scatter plots show the association between the scores in the first adversity factor and the mean BOLD response in the identified clusters for visualization purposes. Abbreviations: dACC, dorsal anterior cingulate cortex; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex, MTG, middle temporal gyrus.

2.2.4.3.2. Specific Adversity Measures

We found similar results for the adversity measures constituting the first adversity factor, namely stressful life events, family adversity, prenatal maternal smoking and self-reported childhood trauma. All identified clusters showed increased activation during successful versus unsuccessful stop trials in individuals with higher adversity scores (all $p < 0.05$, cluster-level corrected, Figure 9). We identified four clusters that showed positive associations with stressful life events, including the left MTG (t=5.13, k=92, p=0.01), right IFG extending to right orbitofrontal cortex, right insula, and right STG (t=4.69, k=113, p = 0.004), superior mPFC extending to left pre-SMA, middle cingulum, and left dACC (t=4.40, k=209, $p < 0.001$), and right insula (t=4.22, k=64, p=0.04). Higher family adversity was linked to higher activation in the left insula extending to left IFG, left orbitofrontal cortex, and left STG (t=5.20, k=174, $p < 0.001$), right insula extending to right STG (t=5.71, k=179, $p < 0.001$), and midbrain (t=4.20, k=91, p=0.01). Maternal smoking was related to higher activation in the left pre-SMA extending to left middle cingulum (t=4.39, k=88, p=0.01), and right middle cingulum extending to right dACC (t=4.34, k=89, p=0.01). Higher scores in the childhood trauma questionnaire were associated with higher activation in right MTG and STG (t=4.45, k=152, $p < 0.001$).

Moreover, maternal stress loaded to the second adversity factor was associated with higher activation in the midbrain (t=4.14, k=119, p =0.003). We did not identify any significant cluster for lower maternal stimulation and obstetric adversity during successful versus unsuccessful stop trials.

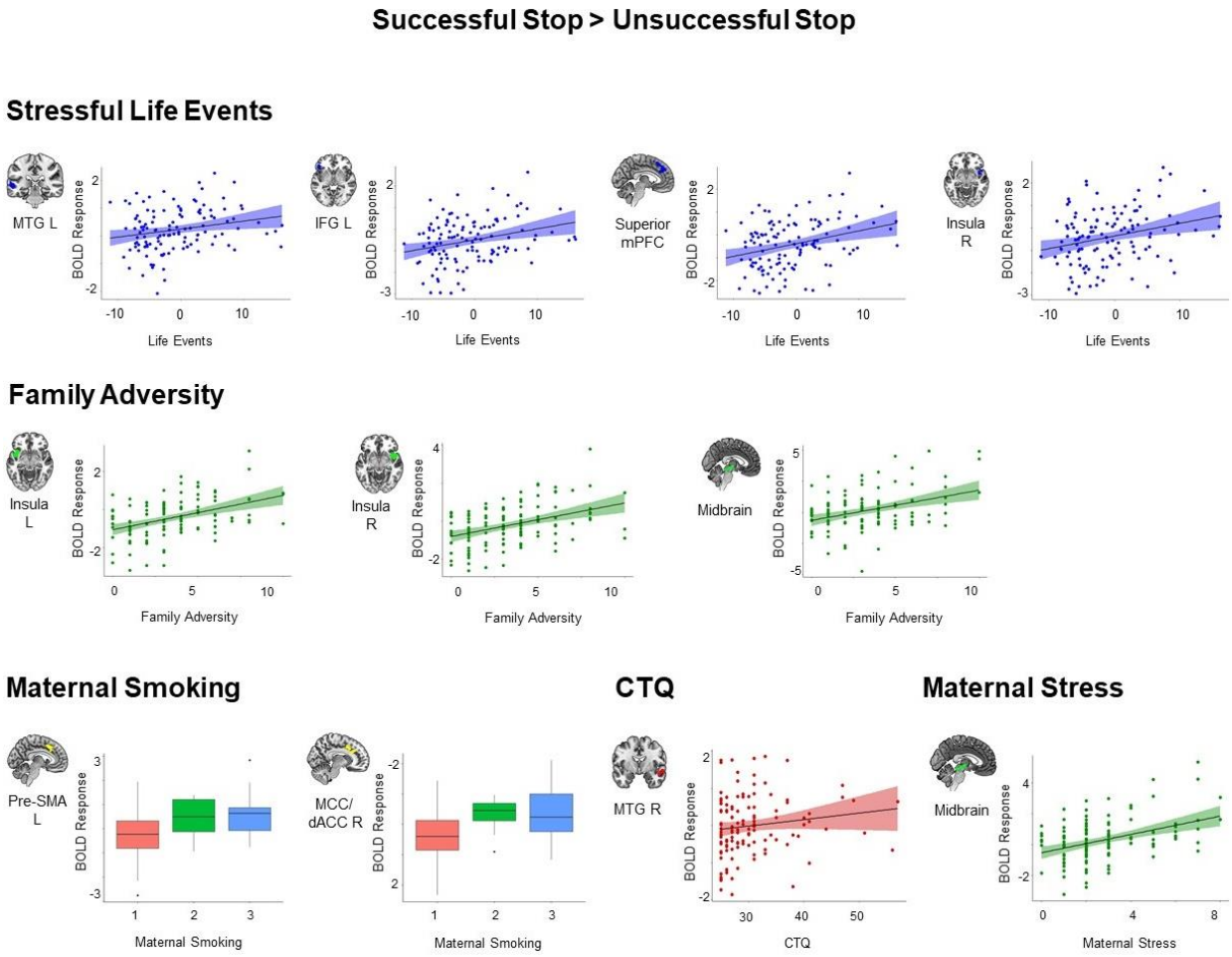

Figure 9. Positive associations between specific adversity measures and brain responses during inhibitory control ($p < 0.05$, cluster-level FWE corrected). Scatter plots show the association between the scores in the specific adversity measures and mean BOLD response in the identified clusters for visualization purposes. Abbreviations: CTQ, Childhood Trauma Questionnaire; dACC, dorsal anterior cingulate cortex; IFG, inferior frontal gyrus; MCC, middle cingulate cortex; MTG, middle temporal gyrus; pre-SMA, pre-supplementary motor area.

Post-hoc analysis on the overlap between adversity and task effects (successful stop versus baseline, unsuccessful stop versus baseline, and successful stop versus unsuccessful stop) was reported in the Supplementary Material S8.

Furthermore, our exploratory sensitivity analyses on the timing effect of adversities revealed that family adversity between the ages of 2 years and 11 years was related to higher activation in insula (all $p < 0.05$, FWE-corrected at cluster level; Table S8 and Figure S9). We found higher activation in MTG at T2, left insula\IFG at T5, and dACC at T7 and T9 during successful stop trials in response to stressful life events (all $p < 0.05$, FWE-corrected at cluster level; Table S9 and Figure S9).

2.2.4.4 Brain-Behavior Association

To explain the meaning of adversity related alterations, we conducted regression analyses with behavioral measures, a task performance measure (i.e., inhibition success) and psychopathology measures, using the successful versus unsuccessful stop trials contrast. Among the significant results, only the regions showing adversity effect were visualized in Figure 10 ($p < 0.05$, cluster-level FWE corrected).

2.2.4.4.1. Inhibition success

Inhibitory control success was associated with lower activation in the left insula (t=4.38, k=69, p =0.03), right insula (t=4.38, k=70, p =0.03), and ACC (t=4.13, k=63, p =0.04) during the successful versus unsuccessful stop trials. These regions also exhibited an overlap with the adversity effect (i.e., the first adversity factor) (Figure 10). Bilateral insula activation also showed an overlap with stressful life events and family adversity (Figure S5). However, the overlap between adversity and lower inhibition success was more visible in the left insula. In addition, inhibitory control success was linked to higher activation in the left inferior occipital gyrus (t=4.74, k=425, p <0.001), right inferior occipital gyrus (t=4.43, k=270, p <0.001), right pre- and postcentral gyrus (t=4.61, k=444, p <0.001), and precuneus/posterior cingulate cortex (t=4.54, k=272, p <0.001).

2.2.4.4.2 Psychopathology

Out of six psychopathology measures, only depressive symptoms were linked to higher activation in the right insula (t=4.96, k=260, p <0.001), left insula (t=4.55, k=70, p =0.03), and ACC (t=3.87, k=72, p =0.03) during the successful versus unsuccessful stop trials. These regions also exhibited an overlap with the adversity effect (Figure 10). The effect of depressive symptoms overlapped with stressful life events and family adversity in bilateral insula (Figure S6) and with inhibition success in the right insula and ACC (Figure S7).

Furthermore, the mediation analysis revealed that right insula activation partially mediated the relationship between the first adversity factor and depressive symptoms (interaction effect (a*b) = 0.33, CI= [0.02 0.76], Figure 11). No other brain region mediated the relationship between the first adversity factor and depressive symptoms or other psychopathology symptoms.

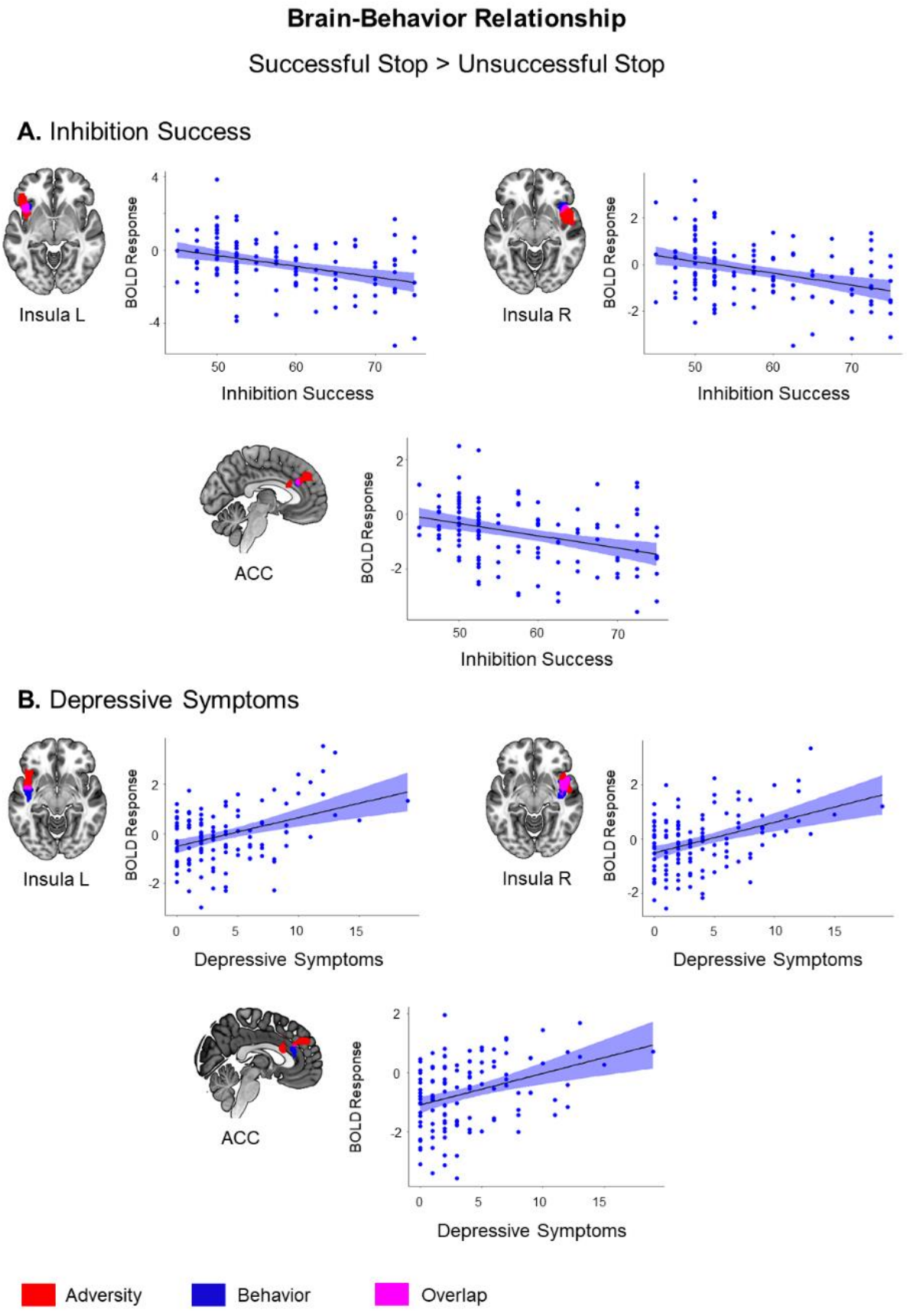

Figure 10. Brain-Behavior Relationship. Brain regions showing associations with inhibition success (A) and depressive symptoms (B) during successful versus

unsuccessful stop trials were visualized in blue color on the brain surface ($p < 0.05$, cluster-level FWE corrected). Inhibition success showed a negative association with BOLD response, while depressive symptoms showed a positive association with BOLD response during successful versus unsuccessful stop trials. Adversity effect and overlap between adversity and behavior were visualized with red and pink color respectively. Scatter plots show correlations between behavioral scores (inhibition success and depressive symptoms) and mean BOLD response extracted from the clusters associated with respective behavior (blue).

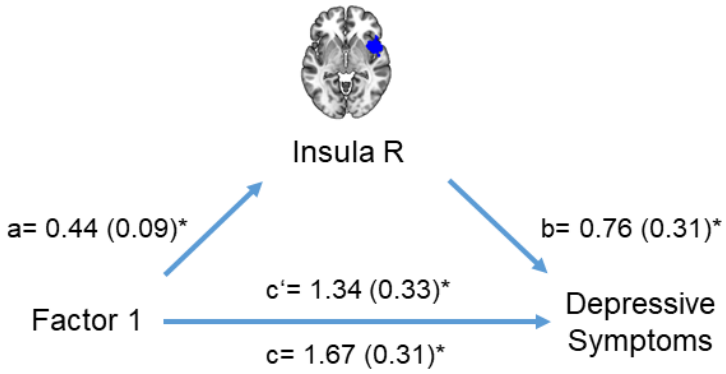

Figure 11. Mediation analysis . The mediation model included right insula activation as a mediator (M) to explain the impact of the first adversity factor (X) on depressive symptoms (Y). Significant paths are shown with asterisk.

2.2.5 Discussion

We here investigated the long-term effect of lifespan adversities on neural inhibitory network during the stop-signal task. Our results showed that lifespan adversities such as prenatal and postnatal psychosocial measures were associated with increased activation in several brain regions including IFG, dACC, insula, and MTG during successful versus unsuccessful stop trials in adults. Furthermore, increased activation in the insula and dACC was related to lower inhibition success and higher depressive symptoms. Taken together, our study contributes to the existing literature on adversity and inhibitory control by providing evidence for brain-behavior associations that were not explicitly demonstrated in previous studies. (Lees et al., 2020; Mueller et al., 2010; Ware et al., 2015). Specifically, our findings regarding the stop-signal task and adversity-related neural alterations offer new insights into the neural mechanisms involved. This adds a novel dimension to our understanding of how adversity impacts brain function, particularly in the context of inhibitory control tasks.

The first adversity factor informed by postnatal psychosocial adversities and prenatal maternal smoking was associated with higher insula and dACC activation during successful compared to unsuccessful stop trials. In other words, individuals with higher adversity exhibited lower activation in these regions during the failed inhibition (i.e., unsuccessful versus successful stop trials). This effect was also partially overlapped with the task effect, where we found higher insula and dACC activation during failed inhibition across the participants (Supplementary Material S8). Moreover, we found adversity-related neural alterations in both regions for stressful life events, only in insula for family adversity, and only in dACC for maternal smoking. Our exploratory analysis indicated an increased sensitivity of the insula for adversity during childhood and ACC during young adulthood. Taken together, these results indicate

that insula and dACC activation were lower during failed inhibition in individuals with higher adversity with potentially different sensitive windows.

Insula together with dACC is a part of salience network and involves in error monitoring process (Bastin et al., 2017; Dali et al., 2023; Ham et al., 2013). Previous studies utilizing directional connectivity methods reported a feedforward connectivity from the anterior insula to dACC following an error (Bastin et al., 2017; Ham et al., 2013), suggesting that the anterior insula might be involved in detecting saliency and signaling dACC that more attention is required to optimize a behavior after an error. Thus, reduced neural activation in the insula and dACC during failed inhibition might be related to reduced allocation of attention to errors in individuals with higher lifespan adversity, which in turn might lead to lower post-error behavioral adjustment. Indeed, we found that lower bilateral insula and dACC activation during unsuccessful versus successful trials were related to lower inhibitory control.

Furthermore, lower activation in the insula and dACC during failed inhibition was associated with higher depressive symptoms. Depression-related alterations also overlapped with the adversity effect. Several studies showed that depressed patients have difficulties in error monitoring (Schroder et al., 2013), exhibit altered neural responses in dACC during error monitoring (Malejko et al., 2021; Nixon et al., 2013), and abnormal resting-state salience network connectivity (Manoliu et al., 2014). Taken together, these results suggest that neural alterations in insula and dACC during error monitoring can be a potential vulnerability correlate for depressive symptoms and can be identified in non-clinical risk groups. Interestingly, although executive dysfunctions are assumed to be an important developmental pathway from early life stress to psychopathology in general (Zelazo, 2020) and previous studies have also identified error processing abnormalities in other clinical samples such as ADHD (Albrecht et al.,

2008; Massat et al., 2018), we only found an association with depressive symptoms. This might be related to our sample characteristics such as having lower variance in other psychopathology scales and a higher prevalence of depression in adulthood. Future research should also include clinical groups with adversity exposure to make inferences about the vulnerability aspect.

Higher scores in the first adversity factor as well as stressful life events and family adversity were related to higher IFG activation during successful versus unsuccessful stop trials. This result is compatible with a previous study showing higher IFG activation during inhibitory control in adolescents with early caregiver deprivation (Mueller et al., 2010). Several studies found that IFG plays an important role in behavioral inhibition (Cai et al., 2014; Zandbelt et al., 2013). In line with the literature (Aron & Poldrack, 2006; Duann et al., 2009; Rubia et al., 2003), we found that IFG was more active during successful stop trials compared to both go trials and unsuccessful stop trials across the participants. However, the adversity effect as well as inhibition success did not overlap with increased IFG activation (Supplementary Material S8). Therefore, our results do not indicate that higher IFG activation in individuals with higher adversity is linked to higher inhibitory control. Moreover, enhanced IFG activation is not only found in inhibitory control tasks but also in several attentionally demanding tasks (Erika-Florence et al., 2014; Hampshire et al., 2010). In addition, IFG activation is found to be modulated by task difficulty during the stop-signal task (M. E. Hughes et al., 2013), suggesting higher IFG activation with more difficult stop trials. Indeed, a previous study showed that adolescents with prenatal alcohol exposure exhibited greater activation in several frontal regions with higher task difficulty (Ware et al., 2015). Taken together, higher IFG activation in individuals with higher lifespan

adversity might be related to a compensatory recruitment due to higher attentional demand or task difficulty.

Additionally, we found that higher scores in the first adversity factor were related to higher activation in bilateral MTG during successful versus unsuccessful stop trials. This effect was also present for stressful life events and CTQ. MTG was more active during successful inhibition across the participants (Supplementary Material S8), which is in line with other studies reporting increased activation in temporal regions during response inhibition (Congdon et al., 2010; Steele et al., 2013). However, none of the previous studies reported abnormal MTG activity related to adverse experiences during inhibitory control tasks, although altered MTG activation in relation to adversities was identified in other cognitive tasks such as sustained attention (Lim et al., 2016), working memory task (Philip et al., 2016; Philip, Sweet, Tyrka, Price, Carpenter, et al., 2013), and affective Stroop task (Blair et al., 2019). MTG is considered to be a part of the default-mode network and is associated with several cognitive functions including language processing, semantic memory and reasoning (Xu et al., 2015). However, due to a lack of behavioral associations and limited knowledge of its role in inhibitory control, it is difficult to explain why MTG activation is altered during inhibitory control in individuals with higher adversity.

In terms of specific adversity effects, most neural alterations were observed for stressful life events and family adversity. For maternal smoking, we identified an additional neural alteration in pre-SMA which was not identified in the common adversity factor. Higher maternal smoking was also related to higher dACC activation. With this finding, we replicated our previous work showing altered ACC activation in young adults exposed to prenatal maternal smoking during flanker/no-go task (Holz et al., 2014). Interestingly, higher total CTQ scores were only linked to higher MTG

activation. We did not identify another region showing altered activation in relation to self-reported childhood trauma. However, these results must be interpreted with caution since the sample had low trauma exposure. Lastly, although the literature underscores the importance of parental behavior on cognitive development (Guinosso et al., 2016), we did not find any abnormal activation in individuals with lower maternal stimulation during infancy. However, our maternal sensitivity variable measures the socioemotional component of mother-infant interactions. Providing a cognitively rich environment (e.g., books, activities) can have different consequences on cognitive development than simply being emotionally available for the child. Therefore, the effect of cognitively stimulating home environment on executive functioning and brain responses should be further investigated by future studies.

To further address the reliability of our results, we investigated adversity-related neural alterations within the inhibitory control network using a longitudinal design that enables examination of long-term effects of adversities on adult brain functioning, a relatively large sample size, and a stringent methodological framework. The latter included comprehensive exclusion criteria for task performance and conservative thresholding, which collectively may enhance the generalizability and reliability of our findings. However, this study includes several limitations and needs to be interpreted with caution. First, although longitudinal studies offer valuable insights into how adverse experiences affect brain functions later in development, they do not provide enough evidence to make causal inferences. We here measured brain responses to inhibitory control only at the age of 33 years, whereas the adversity measures were collected across development. Thus, longitudinal neuroimaging studies are necessary and can offer a better understanding in terms of causality. Second, our exploratory analysis on the timing effect of psychosocial adversities should be interpreted with

caution. Family adversity measures family characteristics that are tend to consistent across development, and it was not assessed beyond childhood. Except for stressful life events, our analysis did not include another adversity measure covering adolescence and adulthood periods. Third, our reliance on the Adult Self-Report for psychological assessments introduces potential biases inherent in self-report methods. These include recall bias, where participants may not accurately remember past events or feelings, recency bias, which might lead to overemphasis on recent experiences, and response bias, affecting the authenticity of the responses. We acknowledge these as critical limitations in interpreting our findings, given the retrospective nature of the data collected at each assessment wave. Fourth, we implemented principal component analysis to identify adversity factors that take into account the correlative nature of different adversity measures. Although principal component analysis is helpful to model linear relations, non-linear relationships between variables could exist and be worth investigating. Therefore, future studies can implement machine learning approaches for clustering adversities to offer a better understanding of complex interactions between adversities.

In conclusion, our results indicated that higher psychosocial adversities and prenatal maternal smoking were linked to altered responses during successful versus unsuccessful stop trials in several brain regions that are important for successful response inhibition and error monitoring such as IFG, insula, and dACC. Lower insula and dACC activation during failed inhibition (i.e., unsuccessful versus successful stop trials) was further associated with lower inhibition success and higher depressive symptomology. Taken together, these results suggest that lifespan adversities are related to neural changes potentially heightening the risk of developing

psychopathology. However, this aspect needs to be further examined by future studies using repeated prospective assessments of adversity and neural responses together.

2.3 Study III: The long-term correlates of developmental stress on whole-brain functional connectivity during emotion regulation.

In Revision: Sacu, S., Hermann, A., Banaschewski, T., Gerchen, M.F., & Holz, N.E. (2024). The long-term correlates of developmental stress on whole-brain functional connectivity during emotion regulation. *Translational Psychiatry*.

2.3.1 Abstract

Early life stress is associated with alterations in brain function and connectivity during emotion processing and regulation, especially in the fronto-limbic pathway. However, most of the previous studies were limited to a small set of a priori-selected regions of interest and did not address the impact of stress timing on functional connectivity. Using data from a longitudinal birth cohort study (n=161, 87 females), we investigated the associations between different time point of exposure to stress and functional connectivity. We measured stressful life events across development and grouped into four developmental stages: prenatal/newborn, infancy, childhood, and adolescence. All participants completed an fMRI-based emotion regulation task at the age of 33 years. Task-dependent directed functional connectivity was calculated using whole-brain generalized psychophysiological interactions. The association between life stress and connectivity was investigated within a multiple regression framework. Our findings revealed two potential sensitive periods for the long-term impact of stress on functional connectivity in the adult brain. Prenatal stress was associated with lower functional connectivity during emotion regulation in frontal, motor, and subcortical regions, whereas childhood stress was related to lower functional connectivity between subcortical and temporal regions. These results suggest that early life stress alters the connectivity of subcortical, frontal, and temporal regions constituting cognitive and limbic networks, which are important for emotion processing and regulation. Future research should replicate and extend the findings regarding sensitive periods by utilizing diverse paradigms in cognitive, social, and emotional domains.

2.3.2 Introduction

Early life stress (ELS) alters brain development (K. E. Smith & Pollak, 2020) and increases the risk of developing psychopathology later in life(McKay et al., 2021). Individuals exposed to ELS often present with emotion regulation difficulties at behavioral (Weissman et al., 2019) as well as neural (VanTieghem & Tottenham, 2018) levels. At the neural level, emotion regulation requires the recruitment of cognitive control regions, such as the prefrontal cortex, and modulation of amygdala activity (Buhle et al., 2014; Underwood et al., 2021). Several previous studies reported altered activity and connectivity of limbic and cognitive control regions in individuals exposed to ELS (Herzberg & Gunnar, 2020). Healthy adults exposed to ELS showed enhanced amygdala activation in response to negative emotional stimuli (Dannlowski et al., 2013; Javanbakht et al., 2015; Kraaijenvanger et al., 2020) and disrupted fronto-limbic connectivity during emotion regulation (Kim et al., 2013; Kraaijenvanger et al., 2023).

However, most of the previous studies investigated alterations only in the fronto-limbic pathway (Gard, 2021). Fronto-limbic pathway plays a vital role in emotion regulation, and abnormal fronto-limbic connectivity was identified in ELS and stress-related psychopathologies (VanTieghem & Tottenham, 2018). However, less is known about global or whole-brain connectivity alterations following ELS (Holz, Berhe, et al., 2023). Moreover, previous research suggest the involvement of several large-scale brain networks in emotion processing and regulation beyond the fronto-limbic pathway, such as salience network (attention allocation, implicit emotion regulation), executive control networks (emotion regulation, goal-directed behavior) and default-mode network (mentalizing, autobiographical memory) (Barrett & Satpute, 2013; Morawetz et al., 2020). Thus, investigating whole-brain connectivity via large-scale brain

networks rather than a small set of regions of interest can bring new insights into the neural embedding of ELS.

The majority of evidence for disrupted large-scale network connectivity following ELS comes from resting-state fMRI literature (Holz, Berhe, et al., 2023). Several studies reported altered resting-state functional connectivity of large-scale brain networks in individuals exposed to adversities (Fadel et al., 2021; Gupta et al., 2017; Herzberg et al., 2021; Huang et al., 2021; Ilomäki et al., 2022; Rakesh et al., 2021). Despite the growing literature on resting-state large-scale network alterations, only one previous study investigated whole-brain connectivity using an affective paradigm (Cisler et al., 2018). Their findings showed that early life trauma in adolescent girls was associated with more modular but less globally efficient connectivity during the processing of fearful and neutral faces, irrespective of the emotional valance. While these findings provided compelling evidence for global measures of connectivity in adolescents, it is still unclear how ELS is associated with alterations in large-scale brain networks during affective processing in healthy adults.

Recently, there has been a growing interest in identifying sensitive periods, characterized by a time window of increased vulnerability to stress (Gee & Casey, 2015; Gunnar, 2020; Lupien et al., 2009). A sensitive period suggests that stress occurring during different stages in life might have different impacts on a neural system of interest (Y. Chen & Baram, 2016). In line with this, a recent study showed that abuse during childhood, but not during adolescence, was related to intrinsic functional connectivity alterations in several large-scale networks (Korgaonkar et al., 2023). Their findings underscored the importance of the developmental timing of stress (childhood versus adolescence stress) in intrinsic adult brain connectivity. However, studies examining the long-term impact of stressors occurring very early in life (i.e., under age

3) are still scarce. Although several previous works addressed the impact of early life stressors on infant brain connectivity (Brady et al., 2022; De Asis-Cruz et al., 2020; Qiu et al., 2015; Smyser et al., 2010), only one recent study investigated the long-term impact of an very early life stressor (e.g., prenatal maternal anxiety) in adults (Turk et al., 2023). However, to the best of our knowledge, no previous study examined the impact of lifespan stress (i.e., stress occurring at different developmental stages in a large temporal spectrum) on adult brain connectivity.

The current study aimed to investigate the association between life stress and directed functional connectivity during an emotion regulation task in healthy adults using whole-brain generalized psychophysiological interactions (Gerchen et al., 2014). For this purpose, we used a prospectively-collected life stress measure, which covered different stages in life including prenatal, infancy, childhood, and adolescence periods. All participants completed a task-based fMRI and psychopathology measures at the age of 33 years. We hypothesized that ELS would be associated with alterations in emotion and attention networks. In specific, ELS would be associated with alterations in salience, limbic and frontoparietal network connectivity during emotion regulation given the importance of these networks in emotion regulation(Barrett & Satpute, 2013; Morawetz et al., 2020) and identified functional abnormalities in these networks following ELS (Herzberg et al., 2021). We did not put forward a specific hypothesis regarding the direction of changes because of scarce evidence. In addition, we expected that these network alterations would be linked to psychopathology symptoms.

2.3.3 Materials and Methods

2.3.3.1 Participants

The present study was conducted within the framework of the Mannheim Study of Children at Risk, a longitudinal birth cohort study designed to investigate long-term outcomes of early psychosocial and biological risk factors on development (Laucht et al., 2000). The initial sample included 384 children born between 1986 and 1988. The participants were followed from their birth up to the age of 33 years across 11 assessment waves (See Supplementary Fig. S1 for study design). At the last assessment wave (T11), 170 participants had functional MRI data available. Two participants were excluded due to inefficient coverage of the brain surface during the task. Additional seven participants were excluded due to excessive head motion (> 3 mm in transition or 3 degrees in rotation). The final sample included 161 participants (mean age=32.21 years, 87 females). At the time of fMRI assessment, 21 (13%) participants had current psychopathology, which was confirmed by German version of the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997) (see Table 4 for Sample Characteristics).

The study was approved by the ethics committee of the University of Heidelberg. All participants gave informed consent and were financially compensated for their contribution.

Table 4. Study III sample characteristics.

N=161	
Age, M (SD)	32.21 (0.29)
Sex, N (%), Female	87 (54%)
Current psychopathology, N (%)	21 (13%)
Major Depressive Disorder	7 (4.3%)
Anxiety Disorder	8 (5%)
Alcohol and Substance Abuse	4 (2.5%)
Attention Deficit and Hyperactivity Disorder	1 (<1%)
Schizophrenia	1 (<1%)
Internalizing problems (T11), Median (IQR)	7 (12)
Externalizing problems (T11), Median (IQR)	5 (8)

2.3.3.2 Psychological Measurements

2.3.3.2.1 *Stressful Life Events*

Stressful life events were measured from the first assessment wave (age of 3 months) until the last assessment wave (age of 33 years) using a modified version of the Munich Event List (Maier-Diewald et al., 1983). The items of the life stress questionnaire are specifically designed to cover positive and negative stressors relevant to various developmental periods, addressing domains such as partnership, education, work, health, and finance. For each time point, we first calculated total scores based on the frequency of event occurrence. Since the item numbers differed across assessment waves, the total scores were z-transformed for the standardization purpose. Item numbers and raw total scores for each assessment wave were reported in the Supplementary Table S1. To represent developmental stages, we used the following sum scores: prenatal period and newborn (from pregnancy to up to postnatal 3 months), infancy and toddlerhood (three months to 4.5 years), childhood (4.5 years to 11 years), and adolescence (11 years to 19 years) (Monninger et al., 2020). Here, we are interested in ELS only and used the data through adolescence. The sum scores of life events that occurred in the last 12 months prior to the fMRI measurement was

used to control the effect of current life stress on the main analysis. Life events variables showed small-to-moderate correlations between each other and did not correlate with current life stress (Supplementary Table S1).

2.3.3.2.2 Psychopathology

The Adult Self-Report (Achenbach & Rescorla, 2003) was used to assess current symptoms of psychopathology at the time of the fMRI assessment (age 33 years). The Adult Self-Report assesses adaptive functioning, problems, and substance use and includes 126 items rated on a 3-point Likert scale (0= 'not true', 1= 'somewhat or sometimes true', 2= 'very true or often true'). For the current study, we used internalizing and externalizing problems scores only.

2.3.3.2.3 Emotion Regulation Strategies

We measured habitual use of two common emotion regulation strategies (i.e., reappraisal and suppression) using the German version of Emotion Regulation Questionnaire (Abler, B., Kessler, 2009).

2.3.3.3 Experimental Paradigm

We used an adapted and modified version of the block-designed emotion regulation task (Hermann et al., 2017) to examine neural correlates of emotion regulation. The task consisted of three experimental conditions: Look neutral, look negative and regulate (Supplementary Fig. S3). During the look neutral blocks, participants were asked to simply look at neutral images. During the look negative blocks, participants were asked to attend to negative images without trying to change or alter the emotional state elicited by the images. In the regulate blocks, participants were instructed to decrease their negative affect elicited by the negative image using one of two reappraisal strategies (i.e., distancing and rationalizing). Immediately following the experimental block, participants were asked to rate the intensity of their negative affect.

The total task comprised random presentation of four blocks of each condition and lasted for 6 min 37 s.

2.3.3.4 MRI Data Acquisition and Preprocessing

The functional and structural images were acquired on a Siemens Magnetom Prisma Fit (Siemens, Erlangen, Germany) 3T MRI scanner with a standard 32-channel head coil. During the emotion regulation task, 186 volumes were obtained using a gradient echo-planar sequence sensitive to blood oxygen level-dependent (BOLD) contrast (36 slices, TE= 35 ms, TR = 2100 ms, voxel size = 3 × 3 × 3 mm). The first 11 scans were discarded to allow for equilibration of the magnetic field. Preprocessing was performed using SPM 12 and included the following steps: slice-timing correction, realignment, structural and functional image co-registration, segmentation, normalization to the Montreal Neurological Institute (MNI) 152 template, and smoothing. Frame-wise displacement (M=0.14, SD=0.14) was calculated based on six motion parameters to quantify head motion (Power et al., 2014).

2.3.3.5 First Level Analyses

2.3.3.5.1. Generalized-Linear Modelling

Experimental conditions were convolved with a canonical hemodynamic response function using generalized linear modeling implemented in SPM 12. Six motion parameters and time series from white matter and cerebrospinal fluid were entered into the subject-level analysis as nuisance covariates to correct for motion and physiological noise. Additionally, we censored the scans (as well as preceding and following scans) with frame-wise displacement greater than 0.5 mm (Cisler et al., 2018).

2.3.3.5.2 Brain parcellation

Brain parcellation maps are commonly used to identify brain regions for functional connectivity analysis. We here chose Brainnetome atlas (Fan et al., 2016) for parcellation since it allows comprehensive interpretation of results (both regional and network level labelling) and is not limited to cortical regions. In total, the atlas included 246 regions (210 cortical and 36 subcortical regions). Time series were extracted using the first eigenvariate of all voxels within the regional masks using SPM. To be able to interpret results in a broad sense, we further grouped brain regions into the following region categories: Frontal, temporal, occipital, parietal, insular, cingulum, sensory-motor, subcortex, midbrain, and cerebellum. In addition, brain regions were assigned to seven large-scale brain networks (Thomas Yeo et al., 2011). Region-specific results are reported in the Supplementary Material.

2.3.3.5.3 Functional Connectivity Analysis

We used whole-brain psychophysiological interactions (PPI) (Gerchen et al., 2014) to estimate directed whole-brain functional connectivity during the emotion regulation task. PPIs explain regional responses of one brain area in terms of an interaction between the activity of another brain area (seed) and the time course of experimental conditions (task-related changes). Similar to conventional PPI approaches (Friston et al., 1997; McLaren et al., 2012), whole-brain PPI uses a regression model including the psychological term (experimental condition), the physiological term (regional time series of a seed region) and interactions between psychological and physiological terms but calculates connectivity in a whole-brain manner using priori-selected regions. Importantly, whole-brain PPI provides information about directionality (i.e., directed functional connectivity). Therefore, a functional coupling parameter includes seed (e.g., a region sending information) and target (e.g., a region receiving information) regions, which can be expressed as outgoing (i.e., a seed region sends

information/signal to other regions) or incoming (a target region receives information/signal from other regions) connections.

We here calculated a whole-brain (n x n) connectivity matrix for each experimental condition and each participant using whole-brain PPI. The emotion regulation contrast regulate > look negative was used to identify task-dependent stress-related changes in connectivity.

2.3.3.6 Second-Level Analyses

A one-sample t-test was performed using the emotion regulation (regulate > look negative) contrast to identify brain regions showing task effect ($p < 0.05$, family-wise error (FWE) corrected). Multiple regression analysis was performed to find associations between ELS and task-dependent connectivity. Sex, current psychopathology, and current life stress were included in the analysis as covariates of no interest. Network-based statistics (NBS) (Zalesky et al., 2010) with a conservative t-statistic threshold ($t > 3.5$ for positive connections/associations and $t < -3.5$ for negative connections/associations) (Rakesh et al., 2021) was then used to correct for multiple testing problem. In addition, we calculated effect size for each connectivity parameter using Hedge's g, the bias-corrected version of Cohen's d (Gerchen et al., 2021).

2.3.3.7 Brain- Behavior Relationship

To see if a connection parameter is linked to psychopathology (i.e., internalizing and externalizing symptoms), we conducted simple mass univariate analyses using the ordinary least squares approach. We additionally used psychopathology measures collected across the COVID-19 pandemic, which was conducted slightly after the fMRI assessment (2018-2019): April 2020 (n=116), June 2020 (n=111), November 2020

(n=102), and May 2021 (n=84). This allowed us to see if the connectivity alterations can predict future psychological outcomes in stressful environments.

2.3.3.8 Statistical Analysis

Statistical analyses were conducted using IBM SPSS, Version 27. A t-test for dependent samples was performed to see if emotion regulation is successful. Additionally, we conducted several correlation analyses to examine associations between life stress, psychopathology, and regulation success, and habitual use of emotion regulation strategies. Spearman's rank-order correlation test was performed when the assumption are not met. The behavioral results were corrected for multiple testing (i.e., four developmental stages) using false discovery rate (FDR).

2.3.3.9 Replication Analysis

Selection of a brain parcellation map is a subjective process, which could further introduce heterogeneity (Hallquist & Hillary, 2018). Indeed, a recent study showed that parcellation map selection impacts the interpretation of results with regard to individual differences (e.g., poverty, cognitive ability) (Bryce et al., 2021). To reduce this bias in our connectivity analyses, we repeated our analyses using two other commonly used brain atlases: Automated Anatomical Labelling (Rolls et al., 2020) representing anatomical parcellation and Schaefer atlas (Schaefer et al., 2018) representing functional parcellation with similar features (e.g., region number, network assignment).

2.3.3.10 Stress and Habitual Use of Emotion Regulation Strategies

We additionally checked whether habitual use of emotion regulation strategies is related to stress timing, psychopathology, and regulation success during the task.

2.3.4 Results

2.3.4.1 Behavioral Results

Participants rated the intensity of their negative affect higher in the look negative condition (M=4.76, SD=1.28) than in the emotion regulation condition (M=3.38, SD=1.24; *t* (160) = 13.91, p <0.001), showing that emotion regulation was successful at the behavioral level. We also calculated emotion regulation success based on rating score (look negative – regulate negative). Life stress during adolescence was negatively associated with emotion regulation success (r=-0.23, FDR-p=0.012). Life stress during childhood (r_S=0.23, FDR-p=0.012) and adolescence (r_S=0.19, FDR-p=0.038) were associated with higher internalizing symptoms in adulthood. Similarly, life stress during childhood (r_S=0.19, FDR-p=0.028) and adolescence (r_S=0.21, FDR-p=0.028) were associated with higher externalizing symptoms in adulthood.

2.3.4.2 Task-Related Brain Activation

During emotion regulation (regulate > look negative), there was increased activation in several brain regions including frontal cortex (inferior, middle, and superior frontal gyri), parietal cortex (angular and supramarginal gyri), temporal cortex (middle and superior temporal gyri) and cerebellum, whereas insula, superior temporal gyrus and right precentral gyrus showed decreased activation (p < 0.05, FWE -corrected; Figure S4).

2.3.4.3 Developmental Stress and Task-Related Brain Activation

Stress during childhood was related to higher activation in the left fusiform gyrus and cerebellum (k=83, t=4.52, p < 0.05 whole-brain cluster-level corrected) during emotion regulation (Figure S5). No other stress measure was significantly associated with the brain activation.

2.3.4.4 Task-Dependent Connectivity

During emotion regulation, we found decreases in functional connectivity in several brain regions (p <0.05, NBS-corrected). In total, 233 connections were related to task effect. Most of these task-related alterations were between visual, frontal, parietal, and sensory-motor areas (Figure 12A), corresponding to visual network, default-mode network (DMN), salience network (SN), and sensory-motor network (Figure 12B). Visual network, DAN, and subcortex received input/signal from higher cognitive networks such as DMN, SN, and FPN. These negative influences from high-order cognitive networks might be related to reduced visual and attentional processing of negative images during emotion regulation. The full list of connections with t values and effect sizes can be found in the Supplementary Material Table S3.

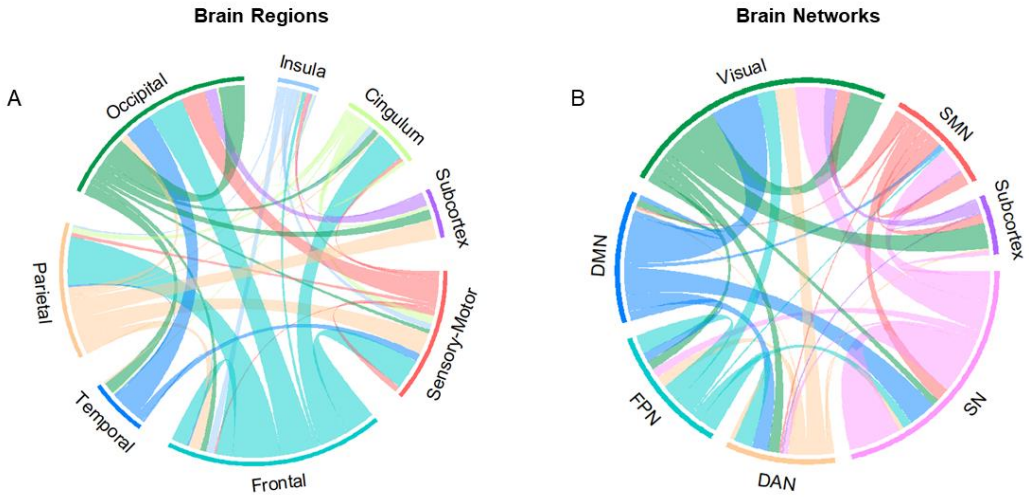

Figure 12. Task-dependent functional connectivity changes during emotion regulation (regulate negative > look negative). In total, 233 connections were related to task effect (i.e., emotion regulation) at corrected level (p < 0.05, NBS-corrected). Each region and network category is assigned to a specific color. Bundle color represents directionality. Connections arising from the source region are depicted with the color of the source region. All results were corrected with network-based statistics.

2.3.4.5 Developmental Stress and Task-Dependent Functional Connectivity

2.3.4.5.1. Prenatal Stress

Prenatal stress and stress shortly after birth was negatively associated with functional connectivity (236 connections), mostly in subcortical and frontal regions ($p < 0.05$, NBS-corrected, Figure 13A, Table S4). Specifically, outgoing connections from frontal regions to subcortex and cingulum and outgoing connections from subcortex to other networks were affected. Subcortical connections included thalamus (incoming and outgoing) and striatum (mostly incoming). At the network level, these alterations corresponded to outgoing connections from frontoparietal network (FPN), dorsal attention network (DAN), and DMN to subcortex and outgoing connections from subcortex to several networks (Figure 13B, Table S4). These alterations did not overlap with main task effects and showed small to medium effect sizes (Hedge's g= [0.28 0.41]).

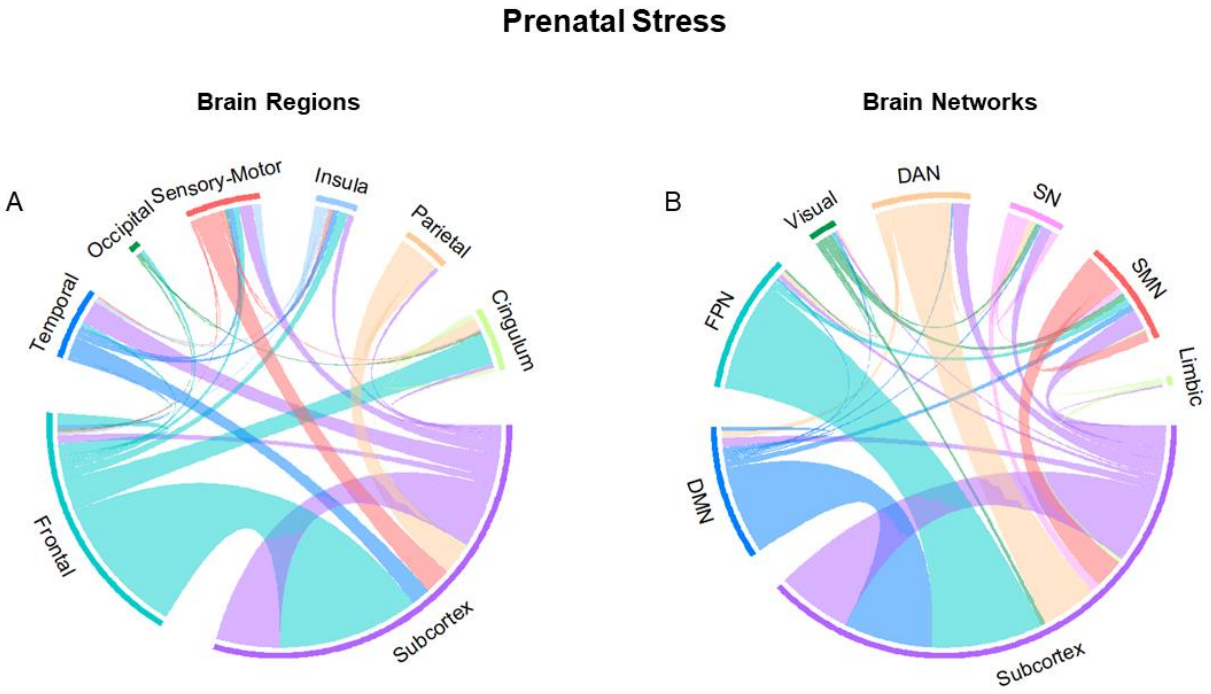

Figure 13. Negative associations between prenatal stress and functional connectivity changes during emotion regulation (236 connections in total). Each region category is assigned to a specific color. Bundle color represents directionality. Connections arising from the source region are depicted with the color of the source region. All results were corrected with network-based statistics ($p < 0.05$).

2.3.4.5.2 Infancy and Toddlerhood Stress

We did not identify any association between life stress during infancy/toddlerhood and functional connectivity during emotion regulation at corrected level.

2.3.4.5.3 Childhood Stress

Childhood stress was negatively associated with functional connectivity (41 connections) in subcortical, temporal and to lesser extent frontal regions (NBS-corrected, Figure 14A, Table S5). Subcortical regions included mostly thalamus. These alterations corresponded to connections from subcortex to several networks including limbic, DMN and attention networks (FPN, DAN) (Figure 14B). Additionally, childhood stress was related altered incoming connections to temporal regions corresponding to

limbic network. These alterations did not overlap with main task effects and showed small effect sizes (Hedge's g= [0.17 0.23]).

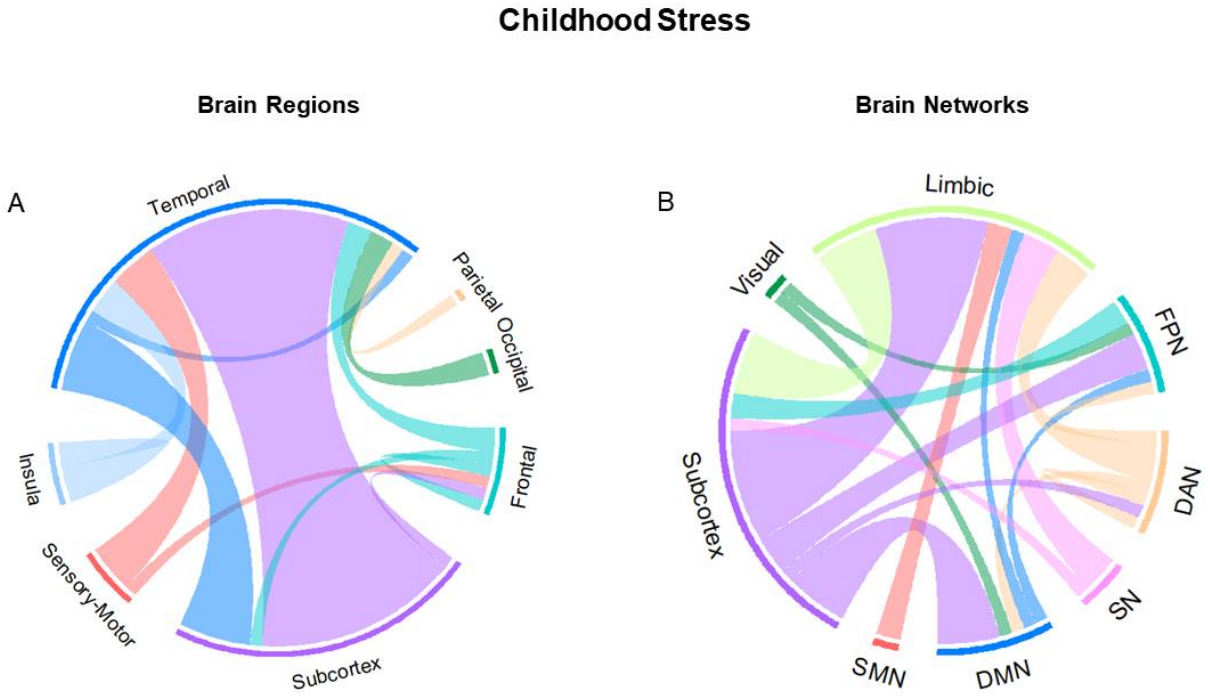

Figure 14. Negative associations between childhood stress and functional connectivity changes during emotion regulation . Each region and network category is assigned to a specific color. Bundle color represents directionality. Connections arising from the source region are depicted with the color of the source region. All results were corrected with network-based statistics ($p < 0.05$).

2.3.4.5.4 Adolescence Stress

Only few connections (n=5) encompassing the visual regions were related to adolescence stress (NBS-corrected, Figure S11, Table S6). These alterations did not overlap with main task effects, showed small effect sizes (Hedge's g= [0.18 0.21]), and were not replicated in other atlases.

2.3.4.6 Brain-Behavior Relationship

Only the connection parameters related to childhood stress were negatively associated with externalizing symptoms at the time of fMRI and across the following three COVID

assessments. We found that 3, 1, 9, and 1 connection parameters were associated with higher externalizing symptoms for each assessment wave respectively, covering the connections between superior temporal gyrus and thalamus mostly (Table S7, all FDR-p < 0.05; Supplementary Fig. S7). The connection from thalamus to inferior temporal gyrus (β= [-4.77 -3.97], all FDR-p <0.05) was replicated across all assessment waves and explained around 6-9% of variation in externalizing symptoms. Brain-behavior associations were most prominent during the second pandemic assessment (June 2020), where the number of COVID cases was high and social interaction was restricted. We did not find any significant association for internalizing symptoms and the connections related to prenatal stress.

2.3.4.7 Replication Analyses

For prenatal and childhood stress, we found similar connectivity changes across the atlases at uncorrected level (p < 0.001). Although some atlases did not survive the NBS correction despite the similar and comparable number of connectivity alterations, reported results were replicable at least for the two atlases at corrected level. We found only a few alterations related to adolescence stress, which survived the correction only for the Brainnetome atlas but not replicated in other atlases even at uncorrected level. See detailed results and discussion in the Supplementary Material S10.

2.3.4.8 Habitual Use of Emotion Regulation Strategies

Habitual use of suppression was associated with higher internalizing symptoms (r_s=0.36, FDR-p < 0.001), lower emotion regulation success (r=-0.23, FDR-p =0.03), and higher adolescence stress (r=0.22, FDR-p =0.02). Both higher adolescent stress (r=-0.18, FDR-p=0.04) and higher suppression (r=-0.24, FDR-p=0.02) were related to lower ratings of negative affect during viewing of negative images. No association was found for habitual use of reappraisal.

2.3.5 Discussion

Here, we investigated long-term associations between ELS and whole-brain functional connectivity by adopting a developmental perspective. Our results revealed two potential sensitive periods for the impact of life stress on adult brain connectivity. During emotion regulation, higher prenatal stress was related to lower functional connectivity from frontal, parietal, and motor regions to the subcortical regions, while higher childhood stress was associated with lower connectivity from subcortex and several cortical regions to temporal regions. Our findings suggest that ELS can be linked to connectivity alterations in the adult brain, covering cognitive, limbic, and subcortical networks that are important for emotion regulation (Morawetz et al., 2020).

The brain is highly plastic early in life and capable of changing its organization to meet environmental requirements (Gao et al., 2017). Indeed, it experiences the most rapid development during the prenatal period and in the first 20 postnatal weeks (Dufford et al., 2021). Neuroimaging studies of the fetal brain showed that functional network organization already starts in utero and continues to mature across development (Thomason et al., 2014, 2015; Turk et al., 2019; Van Den Heuvel et al., 2015). Given the existence of network formation, environmental stressors might potentially alter the functional organization of the brain very early in life. In line with this, fetal programming hypothesis posits that environmental stressors during sensitive windows of fetal development can exert long-lasting influences on health (Kwon & Kim, 2017). However, prenatal stress might be also adaptive, especially when prenatal and postnatal environments are matched in terms of stress, since it gives the opportunity to prepare the developing organism for future challenges (Dufford et al., 2021).

Our results were compatible with a previous study identifying lower frontal connectivity in adults exposed to prenatal maternal anxiety(Turk et al., 2023),

supporting that prenatal stress might indeed be related to long-term changes in brain connectivity. We here found that higher stress exposure during perinatal and newborn periods was associated with widespread connectivity alterations between frontal, parietal, motor, and subcortical regions, corresponding to the cognitive (e.g., FPN, DAN, DMN), sensory-motor and subcortical networks. Most of these alterations encompassed connections from frontal cortex to thalamus and striatum as well as connections from thalamus to striatum, suggesting that connectivity of subcortical regions might be vulnerable to ELS. In line with this, human neuroimaging studies conducted in fetuses and infants provided evidence for altered connectivity of subcortical regions (e.g., amygdala, hippocampus, thalamus) with regard to prenatal stress (Dufford et al., 2021). We here measured stimulus-based stress exposure (i.e., occurrence of a stressful event) rather than perceived/transactional-based stress. Specifically, the studies focusing on more objective aspect of prenatal stress identified altered thalamic connectivity in infants(Brady et al., 2022; Smyser et al., 2010). In line with this, we identified widespread alterations in the thalamo-cortico-striatal pathway, which is essential for learning, behavioral flexibility, attention shifting across cognitive, limbic and sensorimotor modalities (Morris et al., 2016; J. B. Smith et al., 2022).

Similar to prenatal stress, childhood stress involved the altered connectivity of subcortex. However, while prenatal stress was related to altered incoming connections to subcortical regions, especially from frontal cortex, childhood stress was mostly related to altered outgoing connections from subcortex to temporal regions. Likewise, most of the subcortical connections stem from the thalamus. The thalamus exhibits a protracted trajectory and reaches maturation slower than other subcortical structures (Alex et al., 2024). There are also substantial differences in its connectivity across development (Fair, 2010), which can explain the extended vulnerability of this region

to environmental stressors. However, in contrast to prenatal/newborn stress, we did not find a wide range of alterations in striatal connectivity for childhood stress, implying that the striatum can be vulnerable to stressors very early in development (Sacu, Dubois, et al., 2024; Takiguchi et al., 2015; Thomason et al., 2021). Another striking connectivity pattern related to childhood stress was altered connectivity of temporal regions. In line with this, we found that childhood stress was associated with increased activation in the left fusiform gyrus — an occipito-temporal region, which might reflect enhanced visual processing during emotion regulation. Furthermore, the connectivity alterations related to childhood stress were associated with higher externalizing symptoms at the time of fMRI and across the COVID-19 assessments, indicating that these alterations might increase vulnerability to psychopathology in individuals with higher childhood stress, especially in more stressful environments.

We did not identify any consistent neural marker of adolescence stress during emotion regulation. This result is in line with a previous study showing that abuse experienced during childhood, but not during adolescence, was related to altered functional connectivity in adults (Korgaonkar et al., 2023). These results might indicate that childhood can be a more important developmental stage in terms of long-lasting functional connectivity changes. Another possible explanation for the lack of neural correlates in adolescence can be the stress domain. Our stress measure was primarily based on parental reports and reflected family stress. Findings from a previous study showed that peer-related stress, not ongoing negative life events, altered gray matter volume in adolescents (Tyborowska et al., 2018). Taken together, these results suggest that children might be more sensitive to family stress, whereas social stress might be more important for adolescents.

Importantly, both childhood and adolescent stress were related to higher psychopathology symptoms during adulthood. Adolescence stress was further associated with lower regulation success during the task and higher habitual use of suppression. Our supplemental analysis revealed that lower regulation success can be due to lower ratings of negative affect during passive viewing of negative images, which might be explained by higher use of suppression. Adolescents are highly sensitive to their social environment, therefore, they might be more likely to use suppression to cope with their stress in order to prevent rejection (Larsen et al., 2012, 2013). However, adapting a maladaptive regulation strategy might increase in turn vulnerability to psychopathology, especially to internalizing disorders (Aldao et al., 2010).

The current study has several limitations. First, we measured life stress using predominantly parental reports and used a cumulative stress approach without addressing some important dimensions of stress including chronicity, specificity, and subjective perspective. Self-reported stress or the stress dimensions might be related to distinct neural alterations. Second, the time span for the developmental stages was based on available data in this study. They might not reflect the exact stage of development. Third, recall bias in reporting stressful events might be another issue raised due to the length of the measurement intervals. Fourth, our data is suitable for investigating long-term associations only. Longitudinal neuroimaging approaches are necessary to address the temporal dynamics of relationships to infer causality. Lastly, although we attempted to reduce bias in our findings by using multiple parcellation schemes, there are still several methodological issues that need to be addressed by future studies, such as developing advanced correction techniques for multiple testing correction.

To conclude, we identified several ELS-related connectivity alterations in subcortical, frontal, and temporal regions corresponding to cognitive and limbic networks. Alterations related to prenatal stress might reflect an increased vulnerability of the brain to early stressors given the rapid development and high plasticity of the brain early in life. On the other hand, childhood stress was associated with alterations in multiple domains covering brain function, connectivity, and mental health outcomes, suggesting a more detrimental effect of childhood stress on the brain and behavior in the long term. Although adolescence stress was important in terms of mental health outcomes, we did not identify a reliable neural alteration during emotion regulation. Future research is essential to replicate the current findings regarding the sensitive period in diverse task domains.

3 GENERAL DISCUSSION

The current dissertation investigated how childhood adversities are related to brain functioning and mental health in adulthood by taking into account correlative nature of adversities, integrating sensitive periods, and providing associations between neural responses and behavioral measures. Our findings indicated that exposure to adversities, in combination and individually, have a long-lasting impact on brain systems related to reward learning, behavioral inhibition and emotion regulation. The neural changes in these systems were further associated with higher psychopathology symptoms and mediated the relationship between adversities and psychopathology, suggesting that childhood adversities can increase vulnerability to developing psychopathology via neural alterations.

Study I revealed that the third adversity factor representing lower maternal sensitivity and psychosocial adversities was associated with lower EV signaling in the core reward network, including NAcc, putamen and dACC. EV encoding in the right NAcc further mediated the relationship between the third adversity factor and internalizing symptoms and predicted withdrawn symptoms across the COVID-19 pandemic. Taken together, these findings indicate that early sensory input and stable caregiver interactions are important for reward learning (Gee et al., 2018; Novick et al., 2018). The associations between adversity-related brain alterations and higher psychopathology symptoms further suggested that early adverse experiences can increase the risk of developing psychopathology via neural alterations.

In Study II, we extended previous findings (Lees et al., 2020; Mueller et al., 2010; Ware et al., 2015), by showing that childhood adversities have long-term effects on inhibitory control network and provided evidence for brain-behavior relationship which was not examined previously. Specifically, we found that the first adversity factor

representing postnatal psychosocial adversities and prenatal maternal smoking was associated with increased activation in IFG, pre-SMA, dACC, MTG, and insula during successful versus unsuccessful stop trials. The bilateral insula and dACC activation was further linked to lower inhibition success and higher depressive symptoms, while the right insula activation mediated the relationship between the first adversity factor and depressive symptoms. Insula and dACC are a part of salience network and involve in several cognitive processes, such as attention and error processing (Bastin et al., 2017; Ham et al., 2013). Therefore, lower activation in these regions following failed inhibition (i.e., unsuccessful > successful stop trials) might indicate altered neural processing of errors in individuals exposed to higher psychosocial adversity. The associations between these alterations and higher depressive symptoms further suggests that altered neural processing of errors in individuals exposed to adversities might be a potential vulnerability correlate for psychopathology.

Different from the first two studies, Study III investigated the impact of a single adversity measure, namely stressful life events, on whole-brain functional connectivity during an emotion regulation task. Instead of using a total score covering the lifespan, we here used the stress scores representing different developmental stages (e.g., prenatal, infancy, childhood, and adolescence) to allow examining sensitive periods. Our findings revealed two sensitive periods for adult functional connectivity changes: prenatal/newborn and childhood. Both prenatal and childhood stress were associated with lower functional connectivity of subcortical regions during emotion regulation. Specifically, prenatal stress was associated with lower functional connectivity in frontal, motor, and subcortical regions, whereas childhood stress was related to lower functional connectivity between subcortical and temporal regions. Connectivity alterations related to childhood stress were further linked to higher externalizing

symptoms at the time of fMRI assessment and across the COVID-19 pandemic. Taken together, these findings indicate that higher early life stress alters the functional organization of the adult brain and increases the vulnerability to developing psychopathology.

Overall, Study I and Study II proved that cumulative adversity effects represented by adversity factors are reliably associated with mental health outcomes and neural changes in the long-term, while specific effects are still evident. Findings from Study III showed that timing of stress can be important in terms of long-term associations with functional brain organization. Findings from all three empirical studies supported that adversities have long-term associations with the brain function. Moreover, adversity-related neural changes are related to higher psychopathology symptoms and mediate the relationship between adversity and psychopathology. Although these findings indicated vulnerability direction, no causal interpretation was possible due to the study design. These findings together with limitations and future directions were discussed below to provide a comprehensive interpretation of research findings.

3.1 Cumulative Adversity Effects

It is well known that adversities tend to occur together and accumulate over time (Holz, Berhe, et al., 2023). However, most of the previous neuroimaging studies investigated the impact of a single adversity measure on neural systems. This might lead to overestimation of the adversity effect since the effect of a single adversity measure is potentially confounded by other co-occurring adverse events. We here used a data reduction technique, which allowed us to take into account the correlative nature of adversities and provided more specificity compared to the classic cumulative risk approach, where different adversities were simply summed up.

The first adversity factor representing psychosocial adversities and prenatal maternal smoking showed consistent associations with all psychopathology measures in adulthood, including general psychopathology measures (e.g., internalizing and externalizing symptoms) and specific DSM-oriented subscales (e.g., depression, ADHD), which might reflect pervasive effect of prenatal and postnatal adversities on mental health. We found similar associations for the third adversity factor but to a smaller extent, suggesting that quality of caregiver interactions are important for mental health outcomes, but their effect might be smaller compared to the major stressors (e.g., stressful events, trauma) or moderated by other environmental variables. These findings proved the usefulness of our adversity approach by showing a link between the identified factors and mental health outcomes. However, it is important to note that our data set mostly included adversity measures from early life. Except for the stressful life events, we did not have any adversity measure covering adolescence period (e.g., peer rejection, bullying). Also, some adversities were not modelled to due to low incidences in our sample (e.g., parental death, institutionalization). We here attempted to provide a realistic and useful framework rather than a concrete and exhaustive adversity model. However, including these diverse adverse experiences can provide additional insights.

In addition, investigating cumulative effects provided more statistical power (Evans et al., 2013). We were able to identify more extensive neural alterations when we used the adversity factors compared to the specific adversity measures. For example, Study I identified lower EV signaling in the right putamen, right NAcc, and pgACC in adults with higher scores in the third adversity factor. Lower maternal stimulation, the major contributor of the third adversity factor, was also related to similar neural effects (i.e., lower EV signaling in the right putamen and pgACC). These results

suggest that co-occurring adverse events might have a greater impact on neural systems rather than a single event exposure. Indeed, the third adversity factor did not take into account only lower maternal sensitivity but also co-occurring psychosocial adversities. A similar conclusion can be drawn for the Study II. We found that the first adversity factor representing psychosocial adversities and prenatal smoking was linked to increased activations in brain regions involving inhibitory control. When we conducted the same analysis with the adversity measures contributing to the first adversity factor, we obtained similar results but to a smaller extent.

Although the adversity factors reflect cumulative effects, they can still carry some specificity since the adversities gathered under an adversity factor can show similarities in terms of exposures. In line with this, the factors reflecting distinct nature of adversities can also be related to alterations in distinct neural systems. For example, we here found that lower maternal sensitivity had a greater impact on the reward system (Study I), whereas the impact of psychosocial adversities was more prominent over the cognitive control system. Given the fact that family is our first environment and we first learn reward contingencies from maternal behavior (e.g., vocal, facial, and motor maternal responses) (Fareri & Tottenham, 2016; Gee et al., 2018; Novick et al., 2018), it is expected to see that maternal behavior would impact reward learning. However, it is still striking to see that these effects can persist into adulthood. On the other hand, psychosocial adversities might have a bigger impact on cognition, since they might hinder accessing the resources that are necessary for cognitive development or impair the cognitive ability of a child because of enhanced stress reactivity in early life (Guinosso et al., 2016). Taken together, our findings showed that considering cumulative effects provides a statistically powerful framework in investigating adversity-related neural changes while still keeping some specific effects.

3.2 Sensitive Period

Study III specifically examined the impact of stress timing on task-based functional connectivity. Stressful life events were consistently collected across 11 assessment waves and covered the events occurring from the prenatal period on, which allowed us to investigate the impact of stress exposure in a large temporal spectrum (e.g., from prenatal period to adolescence). In addition, stress measures showed small-to-moderate correlations. This indicates that our measure of stress exposure is dynamic and shows developmental variations, which makes it an ideal candidate to examine sensitive periods (Bhutta et al., 2023).

Our findings from Study III revealed two sensitive periods of stress exposure in adult functional connectivity: Prenatal/newborn period and childhood. Both prenatal and childhood stress were related to lower subcortical functional connectivity. The involvement of frontal regions was more prominent in prenatal stress, whereas we identified more connectivity alterations involving temporal regions in childhood stress. At network level, these brain regions corresponded to subcortical, limbic, and cognitive-control networks, which are deemed to be important for emotion processing and regulation (Barrett & Satpute, 2013; Morawetz et al., 2020) . Development of the brain (Dufford et al., 2021) and emotion regulation skills (Martin & Ochsner, 2016) expands in a large time period. Therefore, interaction between environment, brain development and current emotion regulation capacity might be responsible for the identified sensitive periods. More longitudinal prospective neuroimaging research is necessary to understand these complex dynamic interactions and their impact on social functioning.

Furthermore, despite the large number of connectivity changes, neither prenatal stress nor connectivity changes related to prenatal stress was associated with adult

mental health outcomes. In contrast, both childhood and adolescence stress were related to higher internalizing and externalizing symptoms, although we did not find any connectivity change related to adolescence stress. These findings can be explained by recency effect (Dunn et al., 2018), which posits that temporarily proximal stressful events have larger impact on mental health, while earlier effects can dissipate or their effect can be moderated by other mechanisms.

In addition to the behavioral associations between childhood stress and psychopathology, connectivity parameters related to childhood stress were also associated with higher psychopathology symptoms (i.e., externalizing symptoms) in adulthood, establishing brain-behavior relationship. However, it is not clear that why we only found association with externalizing symptoms since childhood stress was related to both internalizing and externalizing symptoms, and similar neural changes during emotion regulation were identified in transdiagnostic samples (McTeague et al., 2020). Taken together, our findings suggest that these two sensitive periods might be linked to different processes. The high number of alterations related to prenatal stress can reflect the high plasticity of the developing brain (Dufford et al., 2021; Pu et al., 2017), whereas childhood stress might have more negative consequences on brain development (Korgaonkar et al., 2023) and mental health. Especially, increased awareness of the environment and ongoing development of regulation strategies might put children exposed to higher stress at risk (Crowell, 2021).

Moreover, we identified altered subcortical connectivity for both prenatal and childhood stress. However, striatal connections were observed only for prenatal stress, while thalamic connections were shared across the two sensitive periods. A recent study investigating the maturation pace of subcortical regions reported protracted maturation of the thalamus, which might explain the extended alterations in childhood.

However, the striatum can be more vulnerable to stressors occurring very early in life (Takiguchi et al., 2015; Thomason et al., 2021). Indeed, our findings from Study I supported this hypothesis. We found that lower maternal stimulation at 3 months was associated with lower EV signaling in the striatum. Our exploratory analyses using time-specific adversity measures further revealed that family adversity during infancy and preschool periods was related to lower EV signaling in the striatum. These results were in line with previous works reporting lower striatal activity in children exposed to maltreatment before the age 4 (Takiguchi et al., 2015) and lower striatal connectivity in fetuses exposed to prenatal maternal stress (Thomason et al., 2021). Taken together, these findings suggest the vulnerability of the striatum to early life stressors, which needs to be replicated by future research.

3.3 Long-Term Impact of Adversities

Our findings suggested that adverse childhood experiences have a long-lasting effect on mental health, brain function and connectivity. This was true even for the adversities occurring very early in life, such as lower maternal stimulation at the 3 months of age (Study I) and prenatal/newborn stress (Study III). These long-term effects might be present early in life and persist into adulthood or might manifest themselves later in life (i.e., sleeper effect) (Bick & Nelson, 2016). Unfortunately, we were not able to test these hypotheses since we did not collect longitudinal neuroimaging data covering childhood and adolescence periods.

However, we were able to replicate some of our previous findings, which were reported using the data from the same cohort at the 25-year assessment. For example, Study I found associations between lower EV signaling in the striatum and the third adversity factor. This finding aligns well with the previous study showing reduced striatal activation during the reward anticipation phase in young adults with higher

childhood adversity (Boecker et al., 2014). Furthermore, another previous study reported that higher maternal stimulation was associated with enhanced striatal responses during reward anticipation in young adults with parental psychopathology (Holz et al., 2018), indicating that early high-quality maternal care can buffer negative outcomes of childhood adversities. In addition, Study II found that higher maternal smoking was related to higher dACC activation during the stop-signal task, which replicates the previous study reporting altered ACC activation during flanker/no-go task in young adults exposed to prenatal maternal smoking (Holz et al., 2014). Taken together, consistent findings across different assessment waves support that childhood adversities have a lasting impact on neural responses during adulthood, which aligns with evidence of stable effects of lifespan adversities on brain structure across adulthood (Holz, Zabihi, et al., 2023).

Furthermore, our findings were in line with the previous studies conducted in adolescent samples. Lower EV signaling in the striatum and prefrontal cortex was observed in adolescents exposed to maltreatment (Gerin et al., 2017) and poverty (Palacios-Barrios et al., 2021). Previous studies using the stop-signal task have consistently reported increased activation in frontal regions in adolescents with adverse childhood experiences (Lees et al., 2020; Lim et al., 2015; Mueller et al., 2010; Ware et al., 2015). Combined with our findings, these findings suggest that adversity-related neural alterations are present early in life and can persist into adulthood. Long-lasting negative outcomes, therefore, necessitate developing effective prevention and intervention strategies for children at risk to support normative brain development following adverse experiences.

Several biological mechanisms have been proposed to explain lasting impact of adversities, including dysregulation of hypothalamic pituitary adrenal (HPA) axis,

increased inflammation and epigenetic changes (Hakamata et al., 2022). Of these, the HPA axis plays a central role in explaining neurobiological mechanisms behind early life adversity and stress-related psychopathologies (Murphy et al., 2022). In response to stress, the HPA axis initiates a cascade of hormonal events, resulting in the release of cortisol- a glucocorticoid hormone that prepares the body to manage stress (S. M. Smith & Vale, 2006). Negative feedback loop in turn monitors and regulates cortisol levels when they become excessive (S. M. Smith & Vale, 2006).

A substantial body of indicates that adverse childhood experiences are associated with dysregulation of HPA axis activity, such as blunted cortisol responses to acute stress (Hakamata et al., 2022; McCrory et al., 2010; Tyrka et al., 2013) and epigenetic modifications of genes involved in glucocorticoid regulation (Tomoda et al., 2024). Consistent with these findings, several studies reported structural and functional changes in brain regions densely populated with glucocorticoid receptors, such as hippocampus, amygdala and prefrontal cortex (Hosseini-Kamkar et al., 2023; Kraaijenvanger et al., 2020; Pollok et al., 2022). However, it is important to note that adversity-related changes are not limited to these brain regions. Altered connectivity between these areas and other related brain regions may contribute to system-level dysfunctions, potentially explaining the distributed neural changes observed (Fornito et al., 2015).

3.4 Brain-Behavior Relationship

Adverse childhood experiences are associated with increased risk of developing psychopathology (Felitti et al., 1998; C. M. Jones et al., 2020; Merrick et al., 2017) and alterations in brain systems related to reward processing, behavioral inhibition and emotion regulation (Bick & Nelson, 2016; Holz, Berhe, et al., 2023; McLaughlin, Weissman, et al., 2019; Vaidya et al., 2024). Interestingly, similar neural alterations

related to reward learning (C. Chen et al., 2015; S. F. White et al., 2013, 2017; S. F. White, Tyler, Erway, et al., 2016), inhibitory control (Aupperle et al., 2016; Bartholdy et al., 2019; Malejko et al., 2021; Massat et al., 2018; Nixon et al., 2013), and emotion regulation (Davis et al., 2018; Eack et al., 2016; Fitzgerald et al., 2019; Paret et al., 2016) were identified in individuals with a wide range of psychopathologies. Overall, these findings lead to a hypothesis, suggesting that adverse childhood experiences might increase the vulnerability for psychopathology and neural responses might mediate the relationship between adversity and psychopathology.

In line with this hypothesis, we identified links between adversity-related neural alterations and current psychopathology symptoms. Study I found that lower EV encoding in the right NAcc mediated the relationship between adversity and internalizing symptoms. Study II showed that decreased bilateral insula and dACC activation during failed inhibition was associated with higher depressive symptoms. Furthermore, right insula activation mediated the relationship between adversity and depressive symptoms. In addition, Study III found a link between connectivity alterations related to childhood stress and externalizing symptoms.

Importantly, these associations were not limited to symptoms measured at the time of fMRI assessment. The COVID-19 pandemic provided us natural stress setting to test if the neural responses can predict future symptomology in stressful environments. We found that lower EV signaling in the right NAcc predicted higher withdrawn symptoms across the COVID-19 pandemic, while the connectivity alterations related to childhood stress were linked to higher externalizing symptoms across the pandemic. Overall, these results suggested that adverse childhood experiences might increase vulnerability to developing psychopathology via neural alterations. However, since our sample consisted of healthy participants mostly, these

results must be replicated in clinical samples. In addition, it is important to note that the brain-behavior relationship can be bidirectional. That is, neural changes may occur before the onset of psychopathology symptoms, but it is also possible that neural changes might be preceded by psychopathology symptoms. Since our design did not allow to investigate causal relationships between neural alterations and behavioral symptoms, future research is necessary to disentangle the directional relationships.

3.5 Limitations and Future Directions

The current dissertation has several limitations. First, although we collected adversity measures prospectively across development, neuroimaging data was available only in adulthood. Therefore, our results do not reflect causal relationships but long-term associations. Recently, excellent initiatives emerged to measure brain development longitudinally, such as the Adolescent Brain Cognitive Development study (Casey et al., 2018) and the Healthy Brain and Child Development study (Jordan et al., 2020). We hope that findings from these initiatives will improve our understanding on how the environment shapes brain development.

In addition, although adversity-related neural alterations indicated vulnerability direction, our sample predominantly consisted of participants without clinical diagnoses, which limits the variation in symptom scores. Future research is necessary to replicate these findings in clinical samples. Moreover, we here did not parse heterogeneity in individuals exposed to adversities. Individuals exposed to adversities might follow distinct developmental trajectories (M. S. Jones & Hoffmann, 2023; Rod et al., 2020; Van Der Vegt et al., 2009), which are not necessarily associated with negative life outcomes (Ellis et al., 2022). Especially, normative modelling can be a promising tool to examine distinct neurodevelopmental trajectories in response to adversity (Marquand et al., 2016).

Furthermore, we here did not investigate the impact of protective factors, which buffer the negative outcomes of exposing to childhood adversities, such as self-esteem and family support (Oshri et al., 2019). Identifying protective factors will further help developing effective prevention and intervention strategies for children at risk and can prevent lasting impact of adversities on brain and behavior. Moreover, longitudinal neuroimaging studies are vital to identify neurodevelopmental processes linking adversity with psychopathology, which can also help to develop brain-based intervention and prevention programs. For example, neurofeedback can be a useful tool to modulate brain function (Goldway et al., 2022) and connectivity (Yamashita et al., 2017) in individuals at risk.

The Mannheim Study of Children at Risk included eleven assessment waves over 33 years with unequal time intervals. Long time intervals between the assessment waves might introduce recall and recency biases for some adversity measures, especially for stressful life events. In addition, most of the measures (e.g., psychopathology, stressful life events) were based on self-reports and therefore, they are subject to response bias. However, it is important to note that most of adversity measures were collected via standard interview procedure, which helped to reduce these biases using several strategies (e.g., follow-up questions, verifying timing information with previous wave responses).

Lastly, although the Mannheim Study of Children Risk provided a comprehensive framework by including a large set of adversity measures across the development, there are several adversity measures, which were not used in the current dissertation (e.g., parental substance abuse) or not available in the data set (e.g., domestic violence, bullying). Investigating the impact of a larger set of exposures would provide additional insights into the neural embedding of early life stress, especially in terms of

individual and cumulative effects. Also, other important aspects of adversities, such as subjective stress perception and chronicity, were not addressed in the current dissertation. Future studies addressing these dimensions will provide a better understanding into stress research.

3.6 Conclusions

Our findings indicated that childhood adversities have long-lasting impacts on brain systems related to reward learning, cognitive control and emotion regulation. Neural alterations in these systems further mediated the relationship between adversities and psychopathology and predicted future symptoms in stressful environments, suggesting that neural alterations might increase the risk of developing psychopathology in individuals at risk. Given the persistent negative effects of adversities, more research should be allocated to preventative strategies to enhance healthy brain development in children at risk.

4 SUMMARY

The current dissertation aimed to investigate the impact of childhood adversities on brain function and connectivity in a cohort of participants followed since their birth by allocating specific attention into cumulative effects and sensitive periods. To address the co-occurrence of adversities, we conducted a principal component analysis using seven adversity measures covering different developmental periods (prenatal maternal smoking, prenatal maternal stress, obstetric adversity, lower maternal stimulation during infancy, family adversity, stressful life events and childhood trauma). This analysis resulted in a three-factor solution (factor 1: postnatal psychosocial adversities and prenatal maternal smoking, factor 2: prenatal maternal stress and obstetric adversity, and factor 3: lower maternal stimulation).

Study I investigated how adverse childhood experiences, in combination (i.e., adversity factors) and in specific (i.e., single adversity measure), affected neural correlates of reward learning (expected value and prediction error signaling). Our findings indicated that the third adversity factor representing lower maternal sensitivity was associated with lower expected value signaling in the core reward network (nucleus accumnbens, putamen, pregenual anterior cingulate cortex). Lower expected value encoding in the nucleus accumbens further mediated the relationship between this adversity dimension and internalizing symptoms and predicted withdrawn symptoms during the COVID-19 pandemic.

Study II examined how adversity factors and their specific contributors affected neural responses during inhibitory control. Our findings showed that the first adversity factor representing postnatal psychosocial adversities and prenatal maternal smoking was related to increased activation in several brain regions involving inhibitory control (inferior frontal gyrus, dorsal anterior cingulate cortex, supplementary motor area, and

insula). Increased activation in the bilateral insula and dorsal anterior cingulate cortex was further related to lower inhibition success and higher depressive symptoms, while the right insula activation mediated the relationship between the first adversity factor and depressive symptoms.

Study III investigated the impact of stressful life events on whole-brain functional connectivity during an emotion regulation task by considering the developmental timing of stress (prenatal, infancy, childhood and adolescence stress). Our findings revealed two sensitive periods for adult functional connectivity: prenatal/newborn and childhood periods. Higher stress during the prenatal period and childhood was related to lower functional connectivity between subcortical, frontal and temporal regions, which are important for emotion processing and regulation. In addition, connectivity alterations related to childhood stress were linked to higher externalizing symptoms at the time of fMRI assessment and across the COVID-19 pandemic.

Taken together, these results suggest that adverse childhood experiences have a lasting impact on neural systems related to reward learning, inhibitory control and emotion regulation. The profound link between adversity-related neural alterations and psychopathology symptoms indicates that childhood adversities might increase the risk of developing psychopathology via neural alterations. Given the long-lasting negative effects of adversities, developing more effective prevention strategies for children at risk is necessary to buffer the negative outcomes of adversities on brain development.

5 ZUSAMMENFASSUNG

In der vorliegenden Dissertation sollten die Auswirkungen von Widrigkeiten in der Kindheit auf die Gehirnfunktion und die Konnektivität in einer Kohorte von Teilnehmern untersucht werden, die seit ihrer Geburt beobachtet wurden, wobei kumulative Effekte und sensible Perioden besonders berücksichtigt wurden. Um das gleichzeitige Auftreten von Widrigkeiten zu untersuchen, führten wir eine Hauptkomponentenanalyse mit sieben Widrigkeitsmaßen durch, die verschiedene Entwicklungsperioden abdeckten (pränatales mütterliches Rauchen, pränataler mütterlicher Stress, organische Risiken kurz nach der Geburt, geringere mütterliche Stimulation während der Kindheit, familiäre Widrigkeiten, belastende Lebensereignisse und Kindheitstrauma). Diese Analyse führte zu einer Drei-Faktoren-Lösung (Faktor 1: postnatale psychosoziale Widrigkeiten und pränatales mütterliches Rauchen, Faktor 2: pränataler mütterlicher Stress und organische Risiken kurz nach der Geburt,, und Faktor 3: geringere mütterliche Stimulation).

Studie I untersuchte, wie sich ungünstige Kindheitserfahrungen in Kombination (d. h. Faktoren, die die verschiedenen Widrigkeiten abbilden) und im Einzelnen (d. h. einzelne Widrigkeiten) auf die neuronalen Korrelate des Belohnungslernens (Erwartungswert und Vorhersagefehler) auswirkten. Unsere Ergebnisse zeigten, dass der dritte Faktor, der eine geringere mütterliche Sensibilität darstellte, mit einer geringeren Verarbeitung des Erwartungswerts im zentralen Belohnungsnetzwerk (Nucleus accumnbens, Putamen, prägenitaler anteriorer cingulärer Kortex) verbunden war. Eine geringere Verarbeitung des Erwartungswerts im Nucleus accumbens vermittelte außerdem die Beziehung zwischen dieser Widrigkeitsdimension und internalisierenden Symptomen und sagte zurückgezogene Symptome während der COVID-19-Pandemie voraus.

Studie II untersuchte, wie sich die verschiedenen Faktoren, die die verschiedenen Widrigkeiten abbilden und ihre spezifischen Mitwirkenden auf die neuronalen Reaktionen während der Inhibitionskontrolle auswirken. Unsere Ergebnisse zeigten, dass der erste Faktor, der postnatale psychosoziale Belastungen und pränatales mütterliches Rauchen repräsentierte, mit einer erhöhten Aktivierung in mehreren Hirnregionen verbunden war, die an der hemmenden Kontrolle beteiligt sind (inferiorer frontaler Gyrus, dorsaler anteriorer cingulärer Kortex, supplementäres motorisches Areal und Insula). Eine erhöhte Aktivierung in der bilateralen Insula und im dorsalen anterioren cingulären Kortex stand außerdem mit einem geringeren Inhibitionskontrolle und depressiven Symptomen in Zusammenhang, während die Aktivierung der rechten Insula den Zusammenhang zwischen dem Faktor 1 und depressiven Symptomen vermittelte.

Studie III untersuchte die Auswirkungen belastender Lebensereignisse auf die funktionelle Konnektivität des gesamten Gehirns während einer Emotionsregulationsaufgabe unter Berücksichtigung des Entwicklungszeitpunkts von Stress (pränataler Stress, Stress in der Kindheit und Jugend). Unsere Ergebnisse zeigten, dass es zwei sensible Zeiträume für die funktionelle Konnektivität von Erwachsenen gibt: die pränatale/neugeborene und die Kindheit. Höherer Stress während der pränatalen Periode und der Kindheit war mit einer geringeren funktionellen Konnektivität zwischen subkortikalen, frontalen und temporalen Regionen verbunden, die für die Emotionsverarbeitung und -regulation wichtig sind. Darüber hinaus waren Konnektivitätsveränderungen im Zusammenhang mit Stress in der Kindheit mit höheren externalisierenden Symptomen zum Zeitpunkt der fMRT Erhebung und während der COVID-19-Pandemie verbunden.

Zusammenfassend deuten diese Ergebnisse darauf hin, dass negative Kindheitserfahrungen einen dauerhaften Einfluss auf neuronale Systeme haben, die mit dem Belohnungslernen, der hemmenden Kontrolle und der Emotionsregulation zusammenhängen. Die Verbindung zwischen den durch widrige Umstände bedingten neuronalen Veränderungen und Psychopathologie deutet darauf hin, dass widrige Umstände in der Kindheit das Risiko für die Entwicklung einer Psychopathologie durch neuronale Veränderungen erhöhen könnten. Angesichts der lang anhaltenden negativen Auswirkungen von Widrigkeiten ist die Entwicklung wirksamerer Präventionsstrategien für gefährdete Kinder notwendig, um die negativen Folgen von Widrigkeiten auf die Gehirnentwicklung abzufedern.

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7 SUPPLEMENTARY INFORMATION

7.1 Study I Supplementary Information: Early life adversities are associated with lower expected value signaling in the adult brain

S1 Sample Characteristics

The initial sample included 384 children born between 1986 and 1988. The infants were recruited from two obstetric and six children´s hospitals in the Rhine-Neckar region of Germany. The participants were followed from their birth up to around the age of 33 years (age range: 31.7- 34.5 years) across 11 assessment waves. At the last assessment wave, 256 participants (67%) agreed to participate in the study and completed psychological measurements. fMRI data for the passive avoidance task was available for 170 participants. After the quality check, the sample size was reduced to 156 participants. Fourteen participants were excluded due to inefficient coverage of the brain surface (n=3), excessive head motion (n=4; > 3 mm in transition or 3 degrees in rotation), no understanding of the task (n=1) and technical problems during the task administration (n=6). Included participants (n=156) did not differ from excluded participants (n=14) in terms of sex and adversities. At the time of the fMRI assessment, 22 (14%) participants had current psychopathology including major depressive disorder (n=7), anxiety disorder (n=9) and alcohol and substance abuse (n=5) and attention deficit hyperactivity disorder (n=1), which was assessed using the German version of the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997).

To identify whether any bias introduced due to non-participation, we compared the participants who were included in the current study (n=156) with the participants who dropped out any time since the first assessment wave or the participants who were not able to attend the fMRI assignment at T11 (n=228) using the adversity measures collected at T1. Two sample t-test was performed for the continuous variables. Mann-Whitney U-test was used when the assumptions were not met, and the chi-square test

was performed for the categorical variables. The included participants had lower family adversity (U=-2.14, p <0.05) and lower obstetric adversity (U=-3.94, p <0.001) compared to the participants excluded in the current study. They did not differ in terms of other adversities, specifically not with respect to maternal stimulation.

Table S1.Characteristics of included and excluded participants.

	Excluded (n=228)	Included (n=156)	Test-statistics	p
Sex[a], n, M/F	116/112	69/87	1.64	0.20
Maternal Smoking[a], n, non-/moderate smoker/heavy smoker	161/26/41	116/17/23	0.78	0.68
Maternal Stress, mean (SD)	3.15 (2.14)	2.78 (1.89)	1.75	0.08
Maternal Stimulation[b], mean (SD)	0.20 (2.53)	-0.29 (2.35)	1.95	0.052
Obstetric Adversity[c], mean (SD)	1.38 (1.18)	0.90 (0.94)	-3.94	**<0.001**
Family Adversity (T1)[c], mean (SD)	2.29 (2.27)	1.75 (1.91)	-2.14	**0.032**
Stressful Life Events (T1), mean (SD)	3.95 (2.18)	3.79 (2.52)	0.66	0.51
CTQ (T9) [d], mean (SD)	32.3 (10.33)	30.88 (8.60)	1.32	0.19

[a] Chi-Square test
[b] Higher scores indicated higher maternal stimulation.
[c] Mann-Whitney U test
[d] Sample size for the excluded group dropped to 157 due to the missing data at T9.

S2. Adversity Measures across Development

Prenatal Maternal Smoking

We measured maternal smoking during pregnancy by a standardized interview conducted with mothers at the 3-month assessment (Holz et al., 2014). Mothers were asked about their daily cigarette consumption (1= no, 2= up to 5 per day, 3= more than 5 per day). The score range is 1-5. Of the mothers of participants, 116 (74.36%) were nonsmokers, 17 (10.90%) reported smoking 1 to 5 cigarettes per day, and 23 (14.74%) reported smoking more than five cigarettes per day.

Prenatal Maternal Stress

Prenatal maternal stress was measured at the first assessment wave (age of 3 months) via a standardized parent interview conducted by trained interviewers (Zohsel et al., 2014). Mothers answered 11 questions covering negative experiences (e.g., 'Did you have mood swings/ a depressed mode') and negatively coded positive experiences (e.g., 'Did you look forward to having a baby') during pregnancy. Additionally, mothers were asked about the timing of these experiences (the first and the second/third trimesters). Here, we specifically used the prenatal maternal stress scores for the second/third trimesters since the effect of mid- and late pregnancy on offspring behavior was found to be the largest (Rice et al., 2010). The items were coded dichotomously based on the presence of experience. The score range is 0-8, with higher scores indicating higher prenatal maternal stress.

Obstetric Adversity

Obstetric adversity scores were calculated according to the degree of obstetric complications based on medical reports (Laucht et al., 2000). The score range is 0-4 (0= no risk, 1-2=moderate risk, 3-4= high risk). Sixty-two infants (39.75%) were born full-term, had normal birth weights and had no medical complications. Ninety-four

infants had moderate to high biological risk (moderate = 53.20%, e.g., preterm birth, preterm labor; high = 7.05%, e.g., birth weight < 1500 g, neonatal complications).

Maternal Stimulation

Videotapes of a 10-min standardized nursing and playing situation between mothers and their 3-month-olds were recorded and evaluated by trained raters (interrater reliability: $\kappa>0.83$) using a modified version of the categorical system for micro-analysis of the early mother-child interaction (Jörg et al., 1994). Raters were blind to parental and child risk status. We coded the presence or absence of nine measures of mother-infant interaction behavior (i.e., rating of vocal, facial, and motor responses for maternal stimulation, maternal responsiveness, and infant responsiveness) in 120 five-second intervals. Maternal stimulation included all attempts (vocal, facial or motor) to attract the infant´s attention or to establish contact with the infant. It was coded as present when the baby was gazing at the mother or the behaviors were directed to the child. The scores were z-transformed, and recoded such that higher scores indicated lower maternal stimulation.

Family Adversity

Family adversity scores (Laucht et al., 2000) were calculated based on the presence of 11 adverse family factors covering characteristics of the parents, the partnership, and the family environment in the period from T1 (age of 3 months) to T5 (age of 11 years). The adverse family factors included low education of a parent, overcrowding, parental psychopathology, parental broken home, marital discord, early parenthood, one-parent family, unwanted pregnancy, poor social integration, severe chronic life difficulties, and poor coping skills of a parent. Early parenthood and unwanted pregnancy were measured only at T1. The score range is 0-10 for the current sample, with higher scores indicating higher psychosocial risk.

Childhood Trauma Questionnaire

Childhood Trauma Questionnaire (CTQ) is a self-reported measure of traumatic experiences that occurred in childhood (Bernstein et al., 1994). We here used the German version of CTQ (Wingenfeld et al., 2010) which includes 28 items covering five subscales: emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Responses are quantified on a 5-point Likert scale (1= ‘never true’, 5= ‘very often true’). The total score range is 25-87, with higher scores indicating more severe trauma. We here used total CTQ scores (M=30.84, SD=8.58) as a summary measure of childhood adversity.

Stressful Life Events

We measured stressful life events from the first assessment wave (age of 3 months) until the last assessment wave (age of 33 years) using a modified version of the Munich Event List [MEL] (Maier-Diewald et al., 1983). The MEL is an interview procedure for assessing acute and chronic as well as positive and negative stressors. It covers items regarding parental socio-economic disadvantages, negative health outcomes, and living and environmental conditions. Parents rated the MEL up to the seventh assessment wave (age of 15 years). From the 15-year assessment onwards, participants rated stressful life events themselves. Here, we calculated a sum score based on separate Z-transformed scores from T1 (age of 3 months) to time T11 (age of 33 years), with higher scores indicating more stressful life events.

Table S2. Adversity Measures

Measurement	Measurement Time	Descriptions
Maternal Smoking	T1 (3 months)	Maternal smoking measured daily cigarette consumption of mothers (1= no, 2= up to 5 per day, 3= more than 5 per day) during pregnancy using a standardized interview.
Maternal Stress	T1 (3 months)	Maternal stress was measured using a standardized interview. Mothers answered 11 questions covering negative experiences and reversely coded positive experiences during the second and third trimesters of pregnancy (e.g., 'Did you have mood swings/ a depressed mode?').
Obstetric Adversity	T1 (3 months)	Obstetric adversity included obstetric complications (e.g., low birth weight, preterm birth, medical complications). The score ranged between 0 and 4 (0=no risk, 1-2=moderate risk, 3-4=high risk).
Maternal Stimulation	T1 (3 months)	Maternal stimulation was based on video recordings of mother-infant interactions (10 minutes) in a play and nurse setting. Trained raters evaluated mothers' attempts (vocal, facial or motor) to draw infants' attention. The scores were z-transformed and recoded such that higher scores indicated lower maternal stimulation.
Family Adversity	T1 – T5 (3 months – 11 years)	Family adversity measured the presence of 11 adverse family factors from birth to 11 years such as parental psychopathology, lower parental education, and marital discord.
Stressful Life Events	T1 – T11 (3 months – 33 years)	We measured stressful life events (e.g., presence of several life stressors in different domains such as partnership, education, work, health, and finance) across the development using an adapted version of the Munich Event List (Maier-Diewald et al., 1983). The sum of Z-transformed scores calculated for each time point (T1-T11) was used for the analyses.
Childhood Trauma	T9 (23 years)	Participants reported retrospectively the presence of traumatic childhood experiences using the German version of Childhood Trauma Questionnaire (Wingenfeld et al., 2010) covering five subscales (emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse). Total scores were used for the analyses.

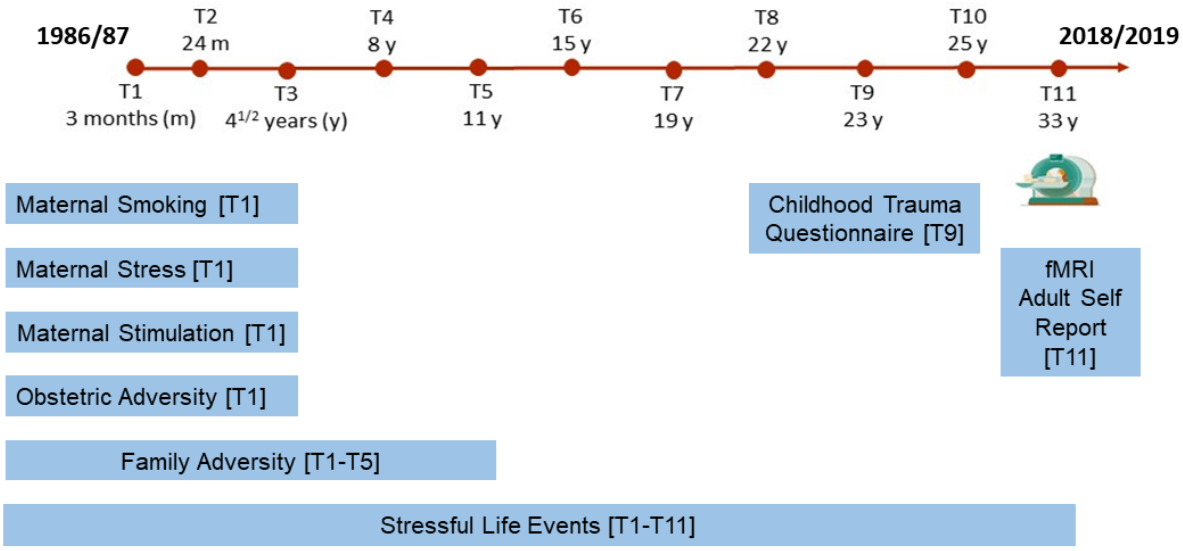

Figure S1. Design of Mannheim Study of Children at Risk.

Table S3. Correlations between adversity measures.

	Maternal Stress	Maternal Smoking	Maternal Stimulation	Obstetric Adversity	Family Adversity	Childhood Trauma Questionnaire	Stressful Life Events
Maternal Stress	-	0.09 [b]	-0.04 [b]	**0.20*[b]**	**0.26** [b]**	0.12 [b]	0.15 [b]
Maternal Smoking		-	-0.01 [b]	-0.02 [b]	**0.31*** [b]**	0.15 [b]	**0.40*** [b]**
Maternal Stimulation			-	-0.01 [b]	**-0.29**[a]**	-0.14 [b]	**-0.20*[a]**
Obstetric Adversity				-	-0.09 [b]	-0.02 [b]	-0.01 [b]
Family Adversity					-	**0.33*** [b]**	**0.59*** [a]**
Childhood Trauma Questionnaire						-	**0.41*** [b]**
Stressful Life Events							-

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$. a= Pearson's correlation test, b= Spearman's correlation test.

Significant correlations are shown in bold font.

S3. fMRI Paradigm

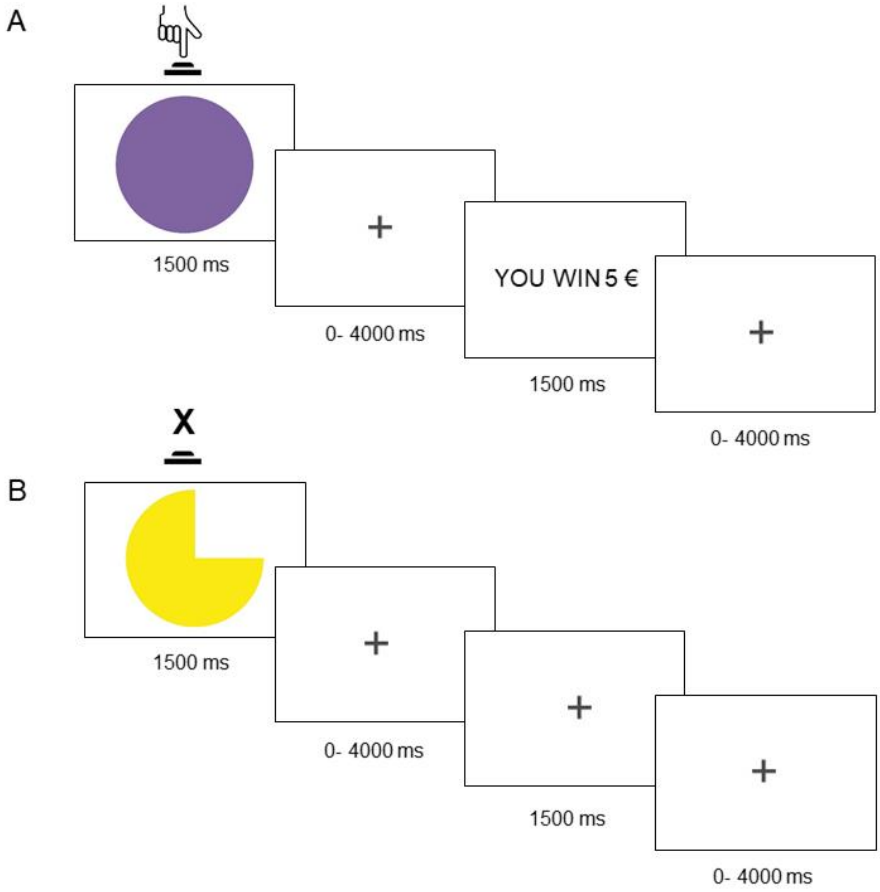

Figure S2. Passive avoidance task. (A) The participant responds to a shape and receives feedback. (B) The participant avoids responding and receives no feedback.

S4. Preprocessing Pipeline

The first five volumes were discarded to allow for equilibration of the magnetic field. The preprocessing steps included slice timing correction of volumes to the middle slice, realignment to the first volume using a rigid body linear transformation, structural and functional image co-registration, segmentation, normalization to the Montreal Neurological Institute (MNI) template, and smoothing using a kernel with a full-width half-maximum of 8 mm.

S5. Computational Modelling

Model Descriptions

To understand the computational mechanisms underlying participants' decision-making, we fit the observed choice data with six different 'families' of reinforcement learning models (Table S4), all of which were based on the classic Rescorla-Wagner model of conditioning (Rescorla & Wagner, 1972). Each model consists of (i) a learning rule, which describes how an expected value is updated on a trial-by-trial basis, and (ii) a choice rule, which describes how expected values are translated into action probabilities. We first describe the learning rule and choice rule in general terms, before elaborating on the differences between each model family.

First, we used the 'delta rule' as the learning rule, which updates the expected value of responding to a stimulus for the upcoming trial, $\mathrm{EV}^{\mathrm{hit}}_{(t+1)}$, based on the feedback observed on the current trial, $\mathrm{FB}_{(t)}$, as follows:

$$\mathrm{EV}^{\mathrm{hit}}_{(t+1)} = \mathrm{EV}^{\mathrm{hit}}_{(t)} + \alpha \times \mathrm{PE}_{(t)} \quad (1)$$

$$\mathrm{PE}_{(t)} = \mathrm{FB}_{(t)} - \mathrm{EV}^{\mathrm{hit}}_{(t)} \quad (2)$$

Here, $\mathrm{PE}_{(t)}$ is the prediction error, which represents the discrepancy between the expected value and the observed feedback, and α ($\alpha \in [0, 1]$) is the learning rate parameter, which determines to what extent the prediction error is used to update the expected value. Higher α values result in a greater reliance on recent feedback, which leads to more heavily fluctuating expected values. Note that if a response is withheld, no feedback is presented and therefore no learning is assumed to occur. Hence, the expected value of not responding to a stimulus is assumed to be fixed at $\mathrm{EV}^{\mathrm{miss}} = 0$.

Second, we used the 'softmax' function as the choice rule, which computes the probability of choosing action i (out of N options) given the expected values of each option as follows:

$$P_{(t)}^{i} = \frac{\exp\left(\beta \times \mathrm{EV}_{(t)}^{i}\right)}{\sum_{j=1}^{N} \exp\left(\beta \times \mathrm{EV}_{(t)}^{j}\right)} \tag{3}$$

Here, β ($\beta \in [0.01, 3]$) is the inverse temperature parameter, which determines the degree of stochasticity in action selection. Larger β values result in more deterministic action selection, where the option with the highest expected value is more likely to be chosen. By contrast, in the extreme case of $\beta = 0$, action selection is purely random such that each option is equally likely to be chosen, regardless of their expected values. Since our modelling approach assumes two mutually exclusive response options – responding or not responding to a stimulus – we can express their corresponding action probabilities, $P_{(t)}^{\mathrm{hit}}$ and $P_{(t)}^{\mathrm{miss}}$, as follows:

$$P_{(t)}^{\mathrm{hit}} = 1 - P_{(t)}^{\mathrm{miss}} = \frac{\exp\left(\beta \times \mathrm{EV}_{(t)}^{\mathrm{hit}}\right)}{\exp\left(\beta \times \mathrm{EV}_{(t)}^{\mathrm{hit}}\right) + \exp(\beta \times \mathrm{EV}^{\mathrm{miss}})} \tag{4}$$

Noting that $\frac{\exp(a)}{\exp(b)} = \exp(a - b)$ and $\frac{1}{\exp(a)} = \exp(-a)$, and recalling that $\mathrm{EV}^{\mathrm{miss}} = 0$, we can simplify the choice rule presented in Equation 4 as a logistic function with growth rate β:

$$P_{(t)}^{\mathrm{hit}} = \frac{\exp\left(\beta \times \left[\mathrm{EV}_{(t)}^{\mathrm{hit}} - \mathrm{EV}^{\mathrm{miss}}\right]\right)}{\exp\left(\beta \times \left[\mathrm{EV}_{(t)}^{\mathrm{hit}} - \mathrm{EV}^{\mathrm{miss}}\right]\right) + 1} \tag{5}$$

$$= \frac{1}{1 + \exp\left(\beta \times \left[\mathrm{EV}^{\mathrm{miss}} - \mathrm{EV}_{(t)}^{\mathrm{hit}}\right]\right)} \tag{6}$$

$$= \left(1 + \exp\left(-\beta \times \mathrm{EV}_{(t)}^{\mathrm{hit}}\right)\right)^{-1} \tag{7}$$

The first model family featured the delta learning rule (Equation 1) in combination with the softmax choice rule (Equation 7), and therefore consists of three parameters: the learning rate α, the expected value of responding for the first trial $\mathrm{EV}_{(1)}^{\mathrm{hit}}$ ($\mathrm{EV}_{(1)}^{\mathrm{hit}} \in [-5, 5]$), and the inverse temperature β.

The second and third model families also used the delta learning rule (Equation 1), but featured extensions of the choice rule to account for a potential bias for or against

responding. Specifically, the second model family featured a constant pressing bias parameter, π, that was added to the expected value of responding, yielding the following choice rule:

$$P_{(t)}^{\text{hit}} = \left(1 + \exp\left(-\beta \times \left[\text{EV}_{(t)}^{\text{hit}} + \pi\right]\right)\right)^{-1} \quad (8)$$

The third model family similarly featured a pressing bias parameter π. However, this parameter was additionally scaled by the proportion of trials remaining in a given fMRI run, so that the value of π decreased linearly across trials within a run. The choice rule of the third model family was thus defined as follows:

$$P_{(t)}^{\text{hit}} = \left(1 + \exp\left(-\beta \times \left[\text{EV}_{(t)}^{\text{hit}} + \pi_{(t)}\right]\right)\right)^{-1} \quad (9)$$

$$\pi_{(t)} = \begin{cases} \pi \times \dfrac{T_{\text{run}} - t}{T_{\text{run}}}, & \text{if run} = 1 \\ \pi \times \dfrac{T_{\text{total}} - t}{T_{\text{run}}}, & \text{if run} = 2 \end{cases} \quad (10)$$

where T_{run} represents the number of trials in a run (i.e., 56) and T_{total} represents the total number of trials in the experiment (i.e., 112). Taken together, the second and third model families each featured four parameters: the learning rate α, the expected value of responding for the first trial $\text{EV}_{(1)}^{\text{hit}}$, the inverse temperature β, and the pressing bias π.

The fourth model family used a valence-dependent delta rule in combination with the extended choice rule introduced for the third model family (Equations 9 – 10). According to the valence-dependent delta rule, positive and negative predictions errors are separately scaled by positive and negative learning rates, α_+ ($\alpha_+ \in [0, 1]$) and α_- ($\alpha_- \in [0, 1]$), respectively:

$$\text{EV}_{(t+1)}^{\text{hit}} = \begin{cases} \text{EV}_{(t)}^{\text{hit}} + \alpha_+ \times \text{PE}_{(t)}, & \text{if PE}_{(t)} > 0 \\ \text{EV}_{(t)}^{\text{hit}} + \alpha_- \times \text{PE}_{(t)}, & \text{otherwise} \end{cases} \quad (11)$$

Taken together, the fourth model family featured five parameters: the positive and negative learning rates α_+ and α_-, the expected value of responding for the first trial $\mathrm{EV}_{(1)}^{\mathrm{hit}}$, the inverse temperature β, and the pressing bias π.

The fifth model family used a simple delta learning rule (Equation 1) in combination with a further extension to the choice rule. Specifically, the choice rule was similar to the choice rule of the third model family (Equations 9 – 10), but allowed for separate pressing bias parameters for the first and second runs, π_1 and π_2, such that the trial-wise pressing bias was computed as follows:

$$\pi_{(t)} = \begin{cases} \pi_1 \times \dfrac{T_{\mathrm{block}} - t}{T_{\mathrm{block}}}, & \text{if block} = 1 \\ \pi_2 \times \dfrac{T_{\mathrm{total}} - t}{T_{\mathrm{block}}}, & \text{if block} = 2 \end{cases} \tag{12}$$

Thus, the fifth model family featured five parameters: the learning rate α, the expected value of responding for the first trial $\mathrm{EV}_{(1)}^{\mathrm{hit}}$, the inverse temperature β, and the pressing biases π_1 and π_2.

Lastly, the sixth model family used the valence-dependent delta rule (Equation 11) in combination with the choice rule introduced for the fifth model family (Equation 12), resulting in 6 parameters: the positive and negative learning rates α_+ and α_-, the expected value of responding for the first trial $\mathrm{EV}_{(1)}^{\mathrm{hit}}$, the inverse temperature β, and the pressing biases π_1 and π_2.

Model Fitting

For each of the six model families described above, we defined several model variants by varying which parameters could be freely estimated and which parameters were fixed to constant values. Across all model families, we considered 26 model variants. Further details regarding the parameter space of each model variant is provided in Table S4.

We used maximum likelihood estimation to fit each model variant to the observed data, on a participant-by-participant basis. Specifically, we defined an objective function for each model family that returned the negative log-likelihood of the data given a proposed set of parameter values. Denoting a given participant's data as $\mathbf{y} = [y_1, y_2, \ldots y_{T_{\text{total}}}]$, where $y_t = 1$ if a response was given on trial t and $y_t = 0$ otherwise, and a proposed set of parameter values as $\boldsymbol{\theta}$, we can express this objective function in general terms as follows:

$$f(\mathbf{y}, \boldsymbol{\theta}) = -\sum_{t=1}^{T_{\text{total}}} \log[\mathcal{L}(\boldsymbol{\theta}|y_t)] \tag{13}$$

$$\mathcal{L}(\boldsymbol{\theta}|y_t) = p(y_t|\boldsymbol{\theta}) = \begin{cases} P_{(t)}^{\text{hit}}, & \text{if } y_t = 1 \\ P_{(t)}^{\text{miss}}, & \text{if } y_t = 0 \end{cases} \tag{14}$$

For each model variant and each participant, we used this objective function to identify the set of parameter values that minimized the negative log-likelihood of the data – that is, the maximum likelihood parameter estimates:

$$\widehat{\boldsymbol{\theta}} = \arg\min_{\boldsymbol{\theta}} f(\mathbf{y}, \boldsymbol{\theta}) \tag{15}$$

This model fitting procedure was performed with bound-constrained minimization using a truncated Newton algorithm, implemented with the minimize function from the optimize package of the SciPy library (Virtanen et al., 2020). Initial values for free parameters were randomly sampled from uniform distributions with parameter-dependent bounds.

Model Selection

To compare the model variants in terms of their goodness of fit, we computed the Akaike information criterion (AIC) and Bayesian information criterion (BIC) as surrogates for the model evidence (i.e., marginal likelihood). For a given participant's

data $\mathbf{y}$ and estimated set of parameter values $\widehat{\boldsymbol{\theta}}$, these quantities are computed as follows:

$$\mathrm{AIC} = 2 \times f\left(\mathbf{y}, \widehat{\boldsymbol{\theta}}\right) + 2k \tag{16}$$

$$\mathrm{BIC} = 2 \times f\left(\mathbf{y}, \widehat{\boldsymbol{\theta}}\right) + k + \log(T_{total}) \tag{17}$$

where k represents the number of free parameters in the model. We computed AIC and BIC values for each model variant and each participant, and then used the mean AIC and BIC values across participants as summary measures of the goodness of fit of each model variant. We selected the model variant with the lowest mean AIC and BIC values as the best model of the data. This was the case for the third model family – that is, the delta learning rule (Equation 1) and an extended softmax choice rule with a trial-dependent pressing bias (Equations 9 – 10) – with all four of its parameters (α, $\mathrm{EV}_{(1)}^{\mathrm{hit}}$, β, and π) estimated as free parameters (Figure S3). As illustrated in Figure S4-S8, the best-fitting model provided an appropriate account of the observed data. We therefore proceeded by extracting the EV and PE time series for each participant, to be used in fMRI analyses.

Parameter Identifiability

For each model variant, we performed a parameter recovery analysis to ensure that its parameters could be identified from observed data. This analysis involves (i) simulating data from the model using a known set of parameter values, (ii) fitting the model to this simulated data and extracting the estimated parameter values, and lastly (iii) comparing the data-generating parameter values with the estimated ('recovered') parameter values. Here, we repeated this procedure 100 times for each model variant, where each repetition serves as a simulated 'participant'. For each repetition, the data-generating parameter values were randomly sampled from uniform distributions with parameter-dependent bounds: $\alpha \in [0, 1]$, $EV_{(1)} \in [-5, 5]$, $\beta \in [0.01, 3]$, $\pi_t \in [-3, 7]$.

For brevity, we focus on the results of the parameter recovery analysis for the winning model. As illustrated in Figure S9, the data-generating parameter values were strongly positively correlated with the corresponding recovered parameter values (Pearson's $r \geq 0.80$). Furthermore, the data-generating values for one particular parameter (e.g., α) were generally uncorrelated with the recovered values for a different parameter (e.g., π). Taken together, these results suggest that, given our experimental design and model fitting procedure, the model parameters are identifiable.

Table S4. Overview of computational models.

Model family		Parameter space		Model evidence	
Learning rule	Choice rule	Free parameters	Fixed parameters	AIC	BIC
Delta rule (α, $EV_{(1)}$)	Softmax function (β)	α	$EV_{(1)} = 0$, $\beta = 1$	116.93	119.65
		β	$\alpha = 0.1$, $EV_{(1)} = 0$	113.33	116.05
		$EV_{(1)}$	$\alpha = 0.1$, $\beta = 1$	116.97	119.69
		α, β	$EV_{(1)} = 0$	111.89	117.33
		α, $EV_{(1)}$	$\beta = 1$	109.74	115.17
		$EV_{(1)}$, β	$\alpha = 0.1$	106.05	111.49
		α, $EV_{(1)}$, β		103.56	111.71
Delta rule (α, $EV_{(1)}$)	Softmax function with pressing bias (β, π)	α, π	$EV_{(1)} = 0$, $\beta = 1$	106.55	111.99
		α, β, π	$EV_{(1)} = 0$	102.95	111.11
		α, $EV_{(1)}$, π	$\beta = 1$	104.05	112.21
		α, $EV_{(1)}$, β, π		99.66	110.54
Delta rule (α, $EV_{(1)}$)	**Softmax function with trial-dependent pressing bias (β, π_t)**	α, π_t	$EV_{(1)} = 0$, $\beta = 1$	106.40	111.84
		α, β, π_t	$EV_{(1)} = 0$	102.44	110.60
		α, $EV_{(1)}$, π_t	$\beta = 1$	101.97	110.13
		α, $EV_{(1)}$, β, π_t		**94.23**	**105.10**
Valence-dependent delta rule (α_+, α_-, $EV_{(1)}$)	Softmax function with trial-dependent pressing bias (β, π_t)	α_+, α_-	$EV_{(1)} = 0$, $\beta = 1$, $\pi_t = 0$	108.14	113.58
		α_+, α_-, β	$EV_{(1)} = 0$, $\pi_t = 0$	104.70	112.85
		α_+, α_-, π_t	$EV_{(1)} = 0$, $\beta = 1$	103.34	111.50
		α_+, α_-, β, π_t	$EV_{(1)} = 0$	100.92	111.80
		α_+, α_-, $EV_{(1)}$, π_t	$\beta = 1$	99.61	110.49
		α_+, α_-, $EV_{(1)}$, β	$\pi_t = 0$	101.76	112.64
		α_+, α_-, $EV_{(1)}$, β, π_t		96.93	110.52
Delta rule (α, $EV_{(1)}$)	Softmax function with block- and trial-dependent pressing bias (β, π_{t1}, π_{t2})	α, β, π_{t1}, π_{t2}	$EV_{(1)} = 0$	99.65	110.52
		α, $EV_{(1)}$, β, π_{t1}, π_{t2}		97.41	111.00
Valence-dependent delta rule (α_+, α_-, $EV_{(1)}$)	Softmax function with block- and trial-dependent pressing bias (β, π_{t1}, π_{t2})	α_+, α_-, β, π_{t1}, π_{t2}	$EV_{(1)} = 0$	97.43	111.02
		α_+, α_-, $EV_{(1)}$, β, π_{t1}, π_{t2}		95.02	111.33

Note. See section S5 for a description of each model parameter. AIC, Akaike information criterion; BIC, Bayesian information criterion. AIC and BIC values correspond to group means. The model variant with the lowest mean AIC and BIC values is highlighted in bold.

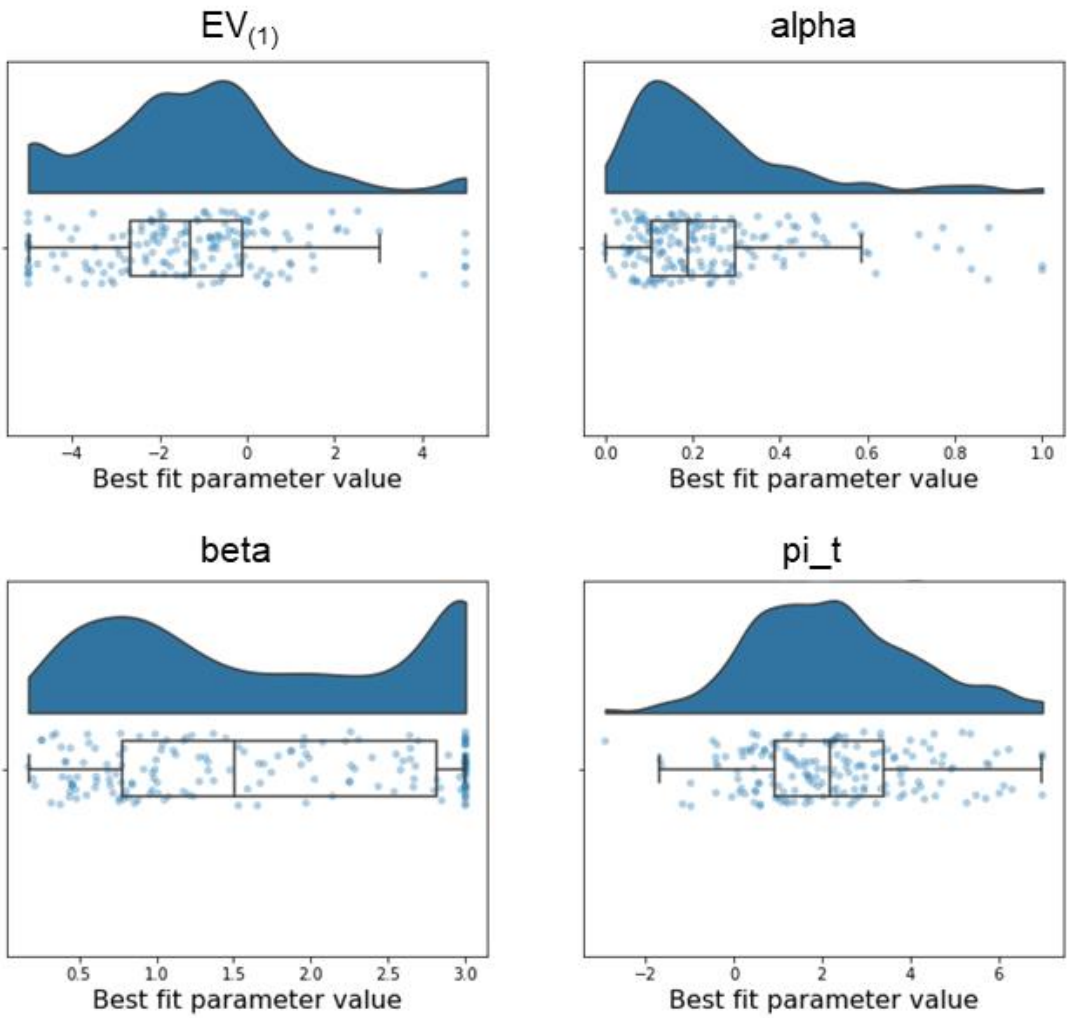

Figure S3. Parameter estimates for the best-fitting model variant.

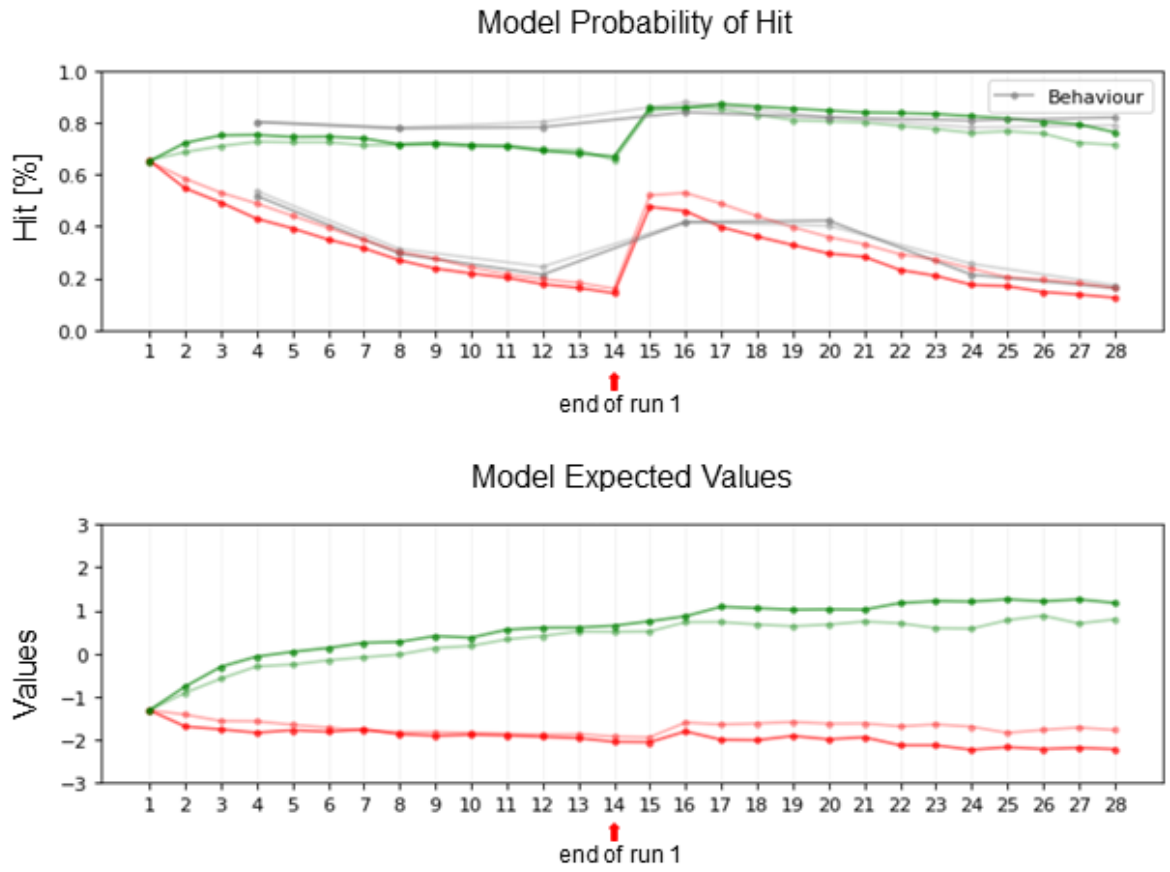

Figure S4. Probability of responding (top panel) and expected values (bottom panel) across trials. The task contained two runs, each featuring an equal distribution of the four cue types (n=14) in each run: high reward (dark green), low reward (light green), low punishment (light red), and high punishment (dark red). Participant averages for each of the four different cues were calculated. For the response probabilities, the observed behavior is illustrated as a moving average with a time window of four cues, with low reward and low punishment in light grey, high reward and high punishment in dark grey. The apparent discontinuity observed between the 14th and 15th trials (upper panel) results from the trial-dependent pressing bias parameter (that is reset between the first and second runs of the task; Equation 10), which significantly enhances model fit compared to variants lacking this run-specific reset.

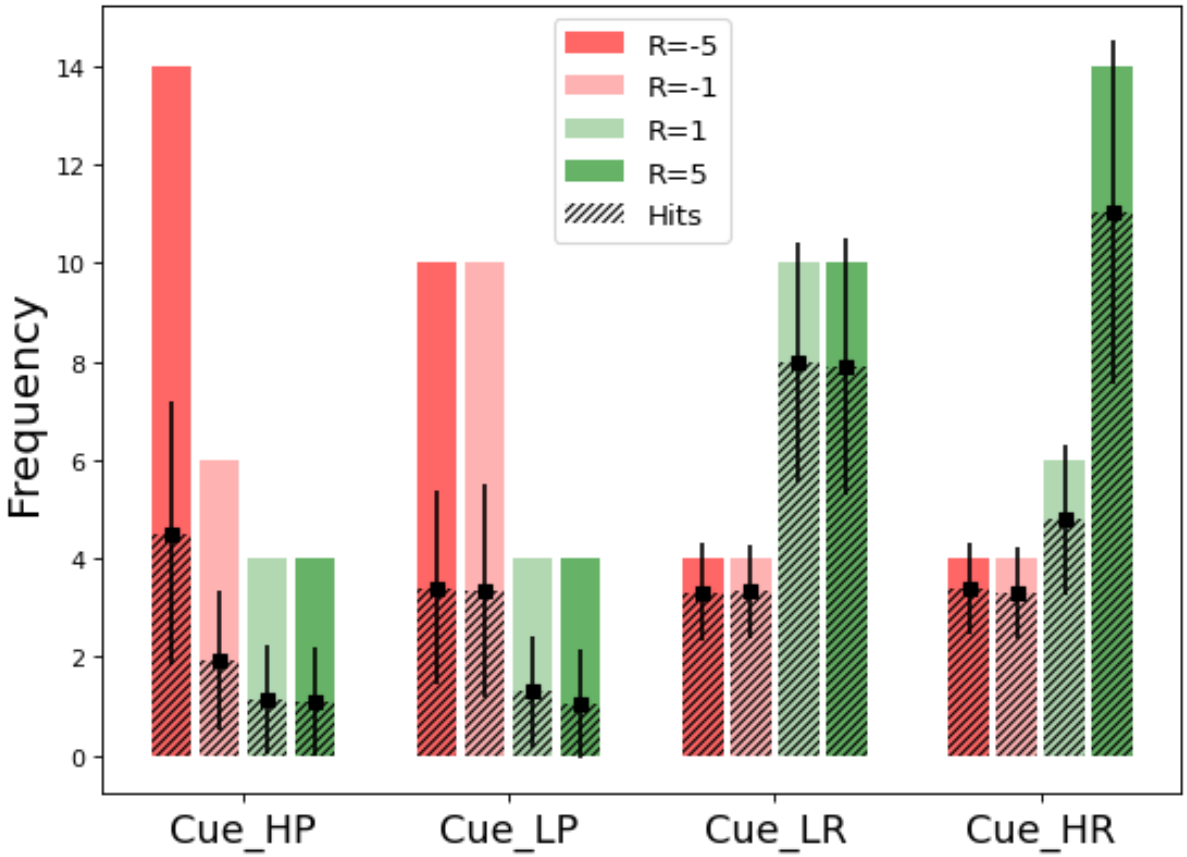

Figure S5. Frequency of four outcomes for each cue type. Red color represents punishment feedback, whereas green color represents reward feedback. Diagonal lines within each box corresponds to average hit responses for each cue type-feedback combination across the participants. Abbreviations: HP, high punishment; LP, low punishment; LR, low reward; HR, high reward.

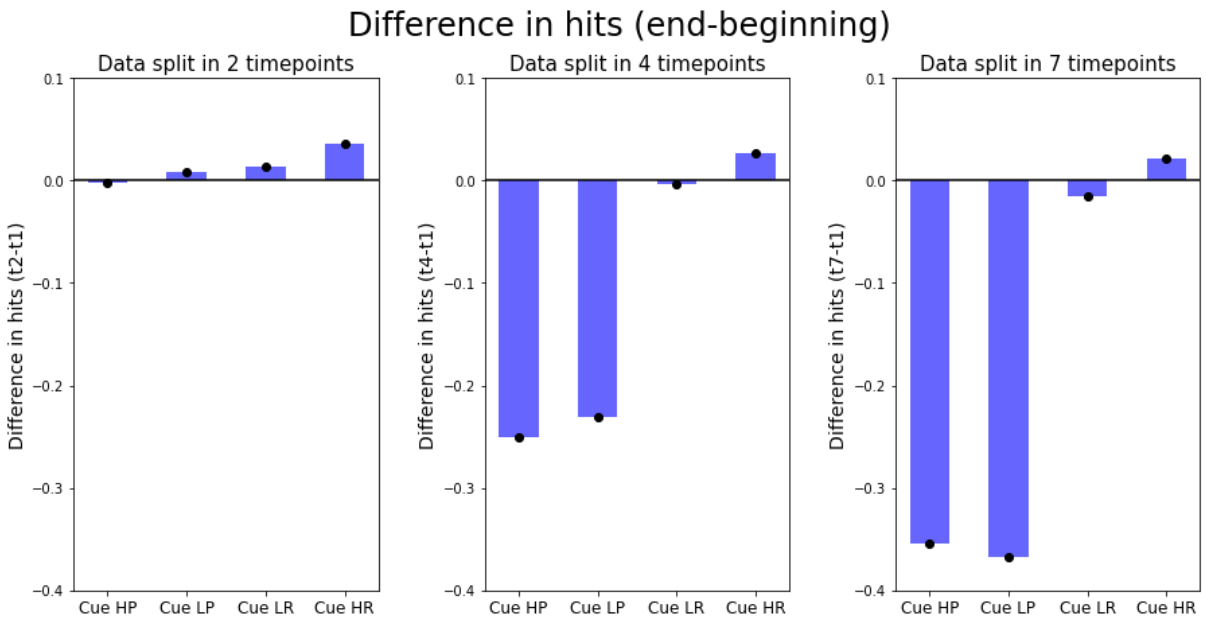

Figure S6. Difference in hits for each cue type. Data was split in two (right panel), four (middle panel), and seven (left panel) time points respectively. The values were averaged across the participants. Abbreviations: HP, high punishment; LP, low punishment; LR, low reward; HR, high reward.

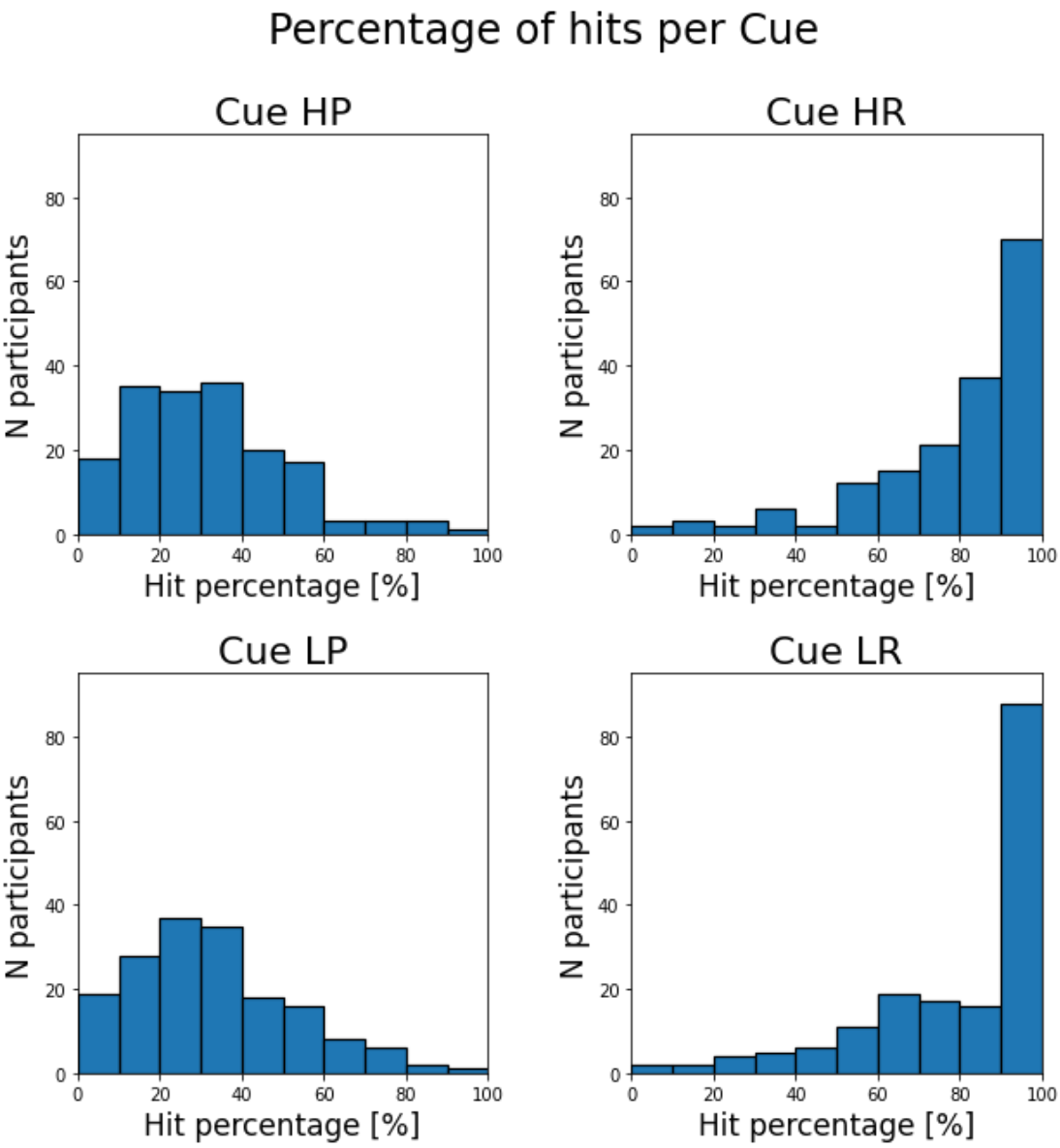

Figure S7. Percentage of hits for each cue type. Abbreviations: HP, high punishment; LP, low punishment; LR, low reward; HR, high reward.

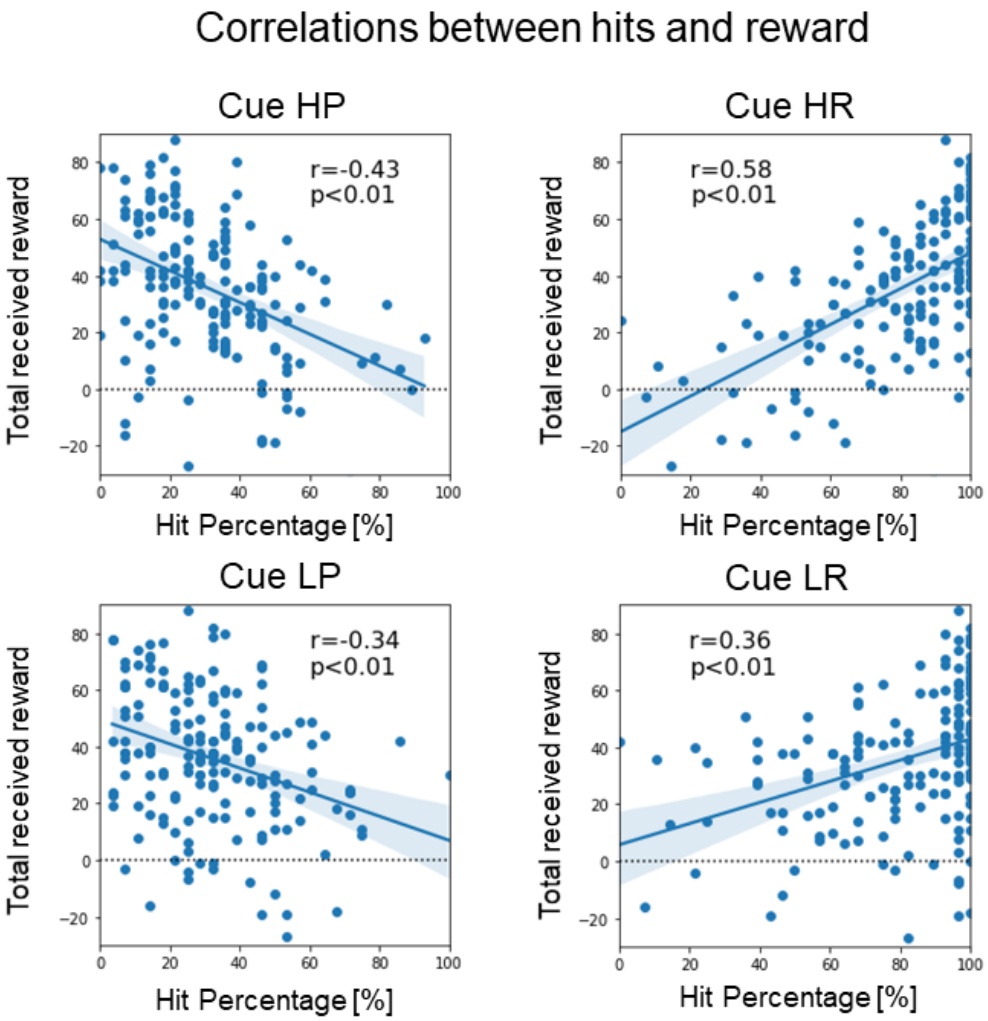

Figure S8. Correlations between total received reward and hit percentage for each cue type. Abbreviations: HP, high punishment; LP, low punishment; LR, low reward; HR, high reward.

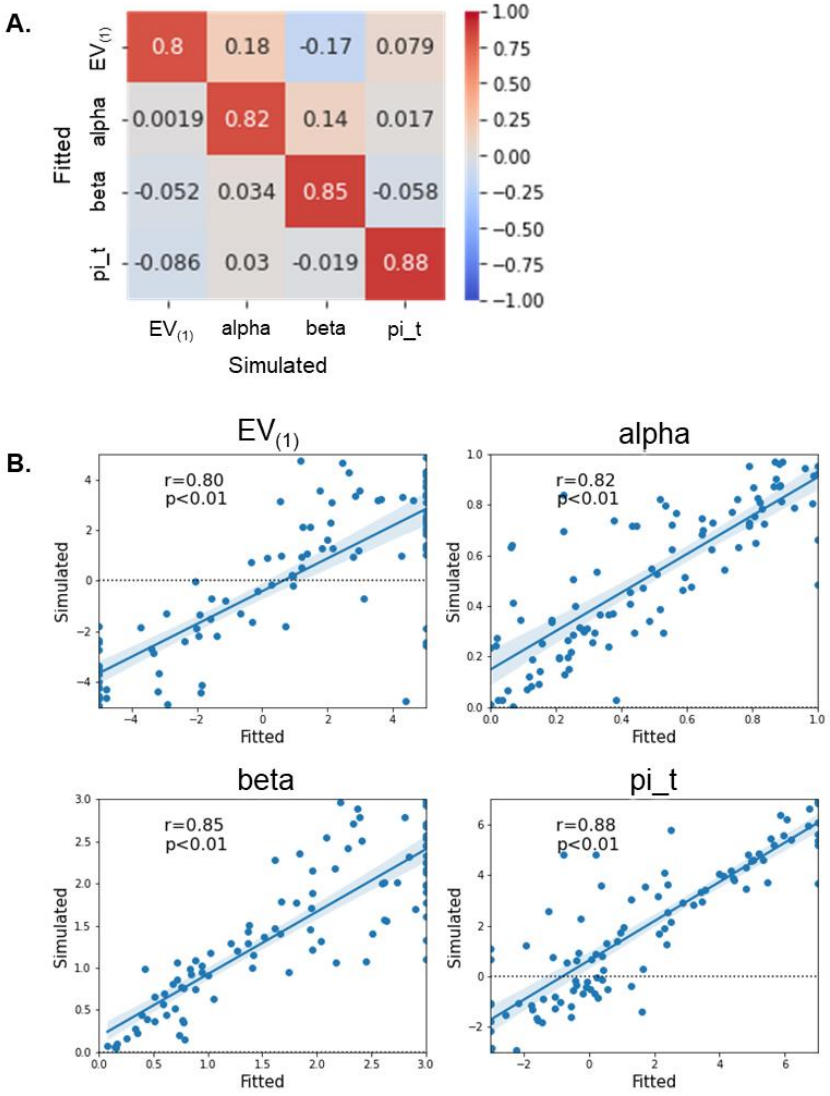

Figure S9. Parameter recovery analysis for the winning model. (A) The confusion matrix illustrates the Pearson correlations between data-generating ('Simulated') and recovered ('Fitted') parameter values across 100 simulated participants. Increasingly red hues correspond to increasingly positive correlations, whereas increasingly blue hues correspond to increasingly negative correlations. The diagonal entries of the matrix are close to one, whereas most of the off-diagonal entries are close to zero, indicating that parameters of the model were identifiable. (B) Scatter plots of simulated and fitted values for each model parameter.

S6. Regions of Interest Analysis

To investigate the associations between three adversity factors and EV/PE signaling, we conducted regions of interest (ROI) analysis in preselected eight brain regions: bilateral striatum (putamen, nucleus accumbens (NAcc), caudate), vmPFC, and pregenual ACC (pgACC). These regions are implicated in EV/PE signaling (Chase et al., 2015) and show abnormalities in individuals exposed to adverse experiences (Cisler et al., 2019; Gerin et al., 2017; Palacios-Barrios et al., 2021). Mean activation from ROI masks were extracted using the MarsBar toolbox (https://www.nitrc.org/projects/marsbar). Striatum subdivision masks were derived from the Melbourne Subcortex Atlas (Tian et al., 2020), whereas the vmPFC and pgACC masks were chosen from a previous study (De La Vega et al., 2016). Multiple linear regression analysis was conducted in SPSS (Version 27). The model included an adversity measure, sex, and current psychopathology. All results were corrected for multiple comparison ($p < 0.05/8=0.00625$). To identify the contribution of specific adversity variables, we repeated the same regression analysis for each adversity measure separately.

S7. Adversity Factors

We identified three adversity factors using principal component analysis (Table S5).

Table S5. The rotated component matrix for three-factor solution.

	Factor 1	Factor 2	Factor 3
Maternal Stress	0.26	**0.76**	-0.02
Maternal Smoking	**0.72**	0.04	-0.38
Maternal Stimulation	0.16	0.02	**0.88**
Obstetric Adversity	-0.14	**0.83**	0.03
Family Adversity	**0.80**	0.10	0.13
Childhood Trauma Questionnaire	**0.59**	0.01	0.35
Stressful Life Events	**0.83**	0.02	0.19

S8. Lifespan Adversity and Psychopathology

Table S6. Spearman's correlations between adversity and psychopathology measures.

	Internalizing Symptoms	Externalizing Symptoms	Depression	Anxiety	Avoidant Personality	Somatic Problems	ADHD	Antisocial Personality
F1	0.39***	0.35***	0.43***	0.34***	0.23**	0.16*	0.29***	0.32***
F2	-	-	-	-	-	-	-	-
F3	0.16*	0.19*	-	-	0.22**	-	0.16*	-
Maternal Stress	0.18*	-	-	-	-	-	-	-
Maternal Smoking	0.19*	-	0.22**	0.16*	-	-	-	-
Maternal Stimulation	-	-	-	-	-0.16*	-	-	-
Obstetric Adversity	-	-	-	-	-	-	-	-
Family Adversity	0.22*	0.20*	0.26**	0.18*	-	-	0.20*	0.19*
Childhood Trauma Questionnaire	0.48***	0.38***	0.44***	0.39***	0.37***	0.16*	0.31***	0.38***
Stressful Life Events	0.36***	0.36***	0.40***	0.33***	0.21**	0.21**	0.28***	0.34***

* p < 0.05 ** p < 0.01*** p < 0.001.. Abbreviations: ADHD, Attention deficit and hyperactivity disorder. Abbreviations: F1, factor 1; F2, factor 2; F3, factor 3.

Table S7. Spearman's correlations between psychopathology measures.

	ADHD	Antisocial Personality	Anxiety	Avoidant Personality	Depression	Somatic Problems	Externalizing Symptoms	Internalizing Symptoms
ADHD	-	0.61**	0.49**	0.46**	0.53**	0.32**	0.73**	0.60**
Antisocial Personality		-	0.34**	0.30**	0.38**	0.21*	0.83**	0.44**
Anxiety			-	0.61**	0.73**	0.35**	0.44**	0.81**
Avoidant Personality				-	0.62**	0.29**	0.36**	0.79**
Depression					-	0.45**	0.47**	0.86**
Somatic Problems						-	0.27*	0.54**
Externalizing Symptoms							-	0.53**
Internalizing Symptoms								-

* p < 0.01
** p < 0.001

S9. Neural Correlates of Expected Value and Prediction Error

We identified robust activation in key brain regions during expected value (EV) and prediction error (PE) signaling such as striatum (caudate, putamen, and nucleus accumbens) and medial prefrontal cortex ($p < 0.05$, whole-brain FWE-corrected). During the cue phase, we found higher EV signaling in the bilateral striatum (caudate, putamen, and nucleus accumbens), midbrain, pre- and postcentral gyrus, supplementary motor area, insula, occipital cortex, and cerebellum (Table S8 & S9). We also found lower EV encoding in bilateral middle frontal gyrus, angular gyrus, left occipital pole, right amygdala/hippocampus, and right inferior temporal cortex (Table S8). During the feedback phase, we found higher PE representation in the striatum (bilateral putamen, bilateral nucleus accumbens, and right caudate), orbitofrontal cortex, superior, medial, and inferior frontal gyrus, occipital cortex, left inferior parietal cortex, and cerebellum (Table S10 & S11) and lower PE representation in the right supplementary motor area and right insula during the feedback phase (Table S10).

Table S8. Peak coordinates of expected value signaling across the whole-brain.

Regions	Hemisphere	Cluster Size	T	MNI Coordinates [x y z]		
Positive Modulations						
Postcentral gyrus Precentral gyrus Supplementary motor area	L	3123	13.99	-54	-22	47
Superior occipital gyrus	R	227	10.34	27	-91	20
Cerebellum	R	97	9.85	15	-64	-46
Striatum	R	121	9.79	9	8	-4
Cerebellum	R	175	9.52	21	-55	-22
Lingual gyrus	L	188	9.38	-9	-85	-7
Striatum	L	104	8.75	-9	8	-7
Insula	R	144	8.63	42	-1	11
Thalamus	L	120	8.09	-15	-19	8
Postcentral gyrus	R	123	7.88	54	-19	20
Lingual gyrus	R	94	7.70	24	-79	-7
Superior occipital gyrus	L	104	7.47	-18	-94	17
Insula	L	21	6.59	-30	23	8
Thalamus	R	10	5.57	6	-16	2
Negative Modulations						
Angular gyrus	R	148	6.62	54	-55	32
Occipital pole	L	39	6.51	-24	-100	-7
Middle frontal gyrus	R	271	6.50	42	29	44
Middle frontal gyrus	L	229	6.34	-39	14	53
Right amygdala	R	22	6.15	27	-7	-19
Inferior temporal gyrus	R	37	5.98	54	-61	41
Angular gyrus	L	45	5.77	-48	-61	41

$p < 0.05$ (whole-brain FWE corrected, cluster size >= 10)

Table S9. Peak coordinates of expected value signaling in the regions of interest.

Regions	Hemisphere	Cluster Size	T	MNI Coordinates [x y z]		
Positive Modulations						
Caudate	L	12	7.25	-6	8	-1
	R	31	9.22	9	11	-1
Putamen	L	14	7.61	-15	5	-10
Nucleus accumbens	L	30	8.75	-9	8	-7
	R	34	9.79	9	8	-4
Anterior cingulate cortex	L+R	6	5.62	0	8	29

$p < 0.05$ (whole-brain FWE corrected)

Table S10. Peak coordinates of prediction error signaling across the whole brain.

Regions	Hemisphere	Cluster Size	T	MNI Coordinates [x y z]		
Positive Modulations						
Striatum (caudate, nucleus accumbens, putamen)	R	112	11.78	12	8	-10
Striatum (caudate, nucleus accumbens, putamen)	L	99	10.17	-12	5	-10
Cerebellum	R	364	9.63	39	-64	-40
Middle occipital gyrus	R	1155	9.10	21	-94	11
Middle frontal gyrus	L	896	7.92	-36	44	-10
Orbitofrontal cortex						
Superior frontal gyrus	L	141	7.18	-21	32	47
Inferior parietal lobe	L	251	6.87	-48	-46	47
Cerebellum	L	143	6.78	-39	-70	-34
Inferior orbital gyrus	R	37	6.41	30	41	-10
Striatum (putamen)	L	64	6.35	-30	-13	8
Posterior cingulate cortex	L	31	5.98	-3	-31	35
Striatum (caudate)	R	13	5.71	15	11	20
Precentral gyrus	R	34	5.62	3	-28	62
Striatum (putamen)	R	14	5.49	33	-4	2
Negative Modulations						
Superior frontal gyrus	R	53	6.97	12	11	65
Insula	R	16	5.66	45	11	2

$p < 0.05$ (whole-brain FWE corrected, cluster size >= 10)

Table S11. Peak coordinates of prediction signaling in the regions of interest.

Regions	Hemisphere	Cluster Size	T	MNI Coordinates [x y z]		
Positive Modulations						
Putamen	L	68	10.04	-15	5	-10
	R	40	10.19	18	8	-10
Nucleus accumbens	L	17	10.17	-12	5	-10
	R	32	11.78	12	8	-10
Anterior cingulate cortex	L	33	6.18	-6	53	-1
Ventromedial prefrontal cortex	L+R	115	6.65	-9	44	-10

$p < 0.05$ (whole-brain FWE corrected)

S10. Supplementary Results

We here reported the results not surviving Bonferroni correction.

Adversity Factors

The third adversity factor was further related to lower EV encoding in right caudate (β=-0.16, p=0.041), left NAcc (β=-0.16, p=0.047), and vmPFC (β=-0.19, p=0.022).

Specific Adversity Factors

Higher maternal stimulation was also linked to lower EV encoding in vmPFC (β=0.18, p=0.030) and right NAcc (β=0.16, p=041).

Sensitive Period

To investigate the timing effect of prospectively collected adversities on EV and PE signaling, we conducted a series of multiple regression analyses. In total, we performed five tests for family adversity (T1-T5) and eleven tests for stressful life events (T1-T11). Stressful life events measured at the last assessment wave (T11) was used as a measure of current stress.

Family adversity measures were not normally distributed and showed moderate to high correlations with each other (Table S12). Stressful life events were roughly normally distributed and showed small to moderate correlations with each other (Table S13). None of the correlations between variables caused to multicollinearity problem ($r > 0.8$).

Table S12. The Spearman's correlations between family adversity measures.

	T1	T2	T3	T4	T5
T1	-	.68***	.61***	.52***	.49***
T2		-	.68***	.53***	.46***
T3			-	.66***	.56***
T4				-	.68***
T5					-

*** $p < 0.001$

Table S13. The Pearson's correlations between stressful life events measures.

	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11
T1	-	.49***	.37***	.20*	.31***	.24**	.19*	.32***	.11	.12	.05
T2		-	.54***	.32***	.27**	.24**	.22**	.30***	.27**	.15	.21**
T3			-	.37***	.22**	.23**	.13	.18*	.24**	.18*	.11
T4				-	.38***	.24**	.09	.14	.20*	.09	.09
T5					-	.46***	.40***	.18*	.23**	.04	.07
T6						-	.26**	.10	.13	.08	-0.01
T7							-	.38***	.36***	.18*	.24**
T8								-	.43***	.35***	.39***
T9									-	.37***	.28***
T10										-	.45***
T11											-

*p <0.05 **p<0.01 ***p<0.001

Our exploratory analyses revealed that higher family adversity at the age of 2 years was linked to lower EV encoding in the right NAcc (β=-0.20, p=0.014), left NAcc (β=-0.21, p=0.0009) and in the right caudate (β-0.18, p=0.026). Moreover, lower EV signaling in right NAcc (β=-0.17, p=0.035), left NAcc (β=-0.17, p=0.034), and right caudate (β=-0.19, p=0.019) was also related to higher family adversity at the age of 4 years.

S11. Zero-Inflated Poisson Model

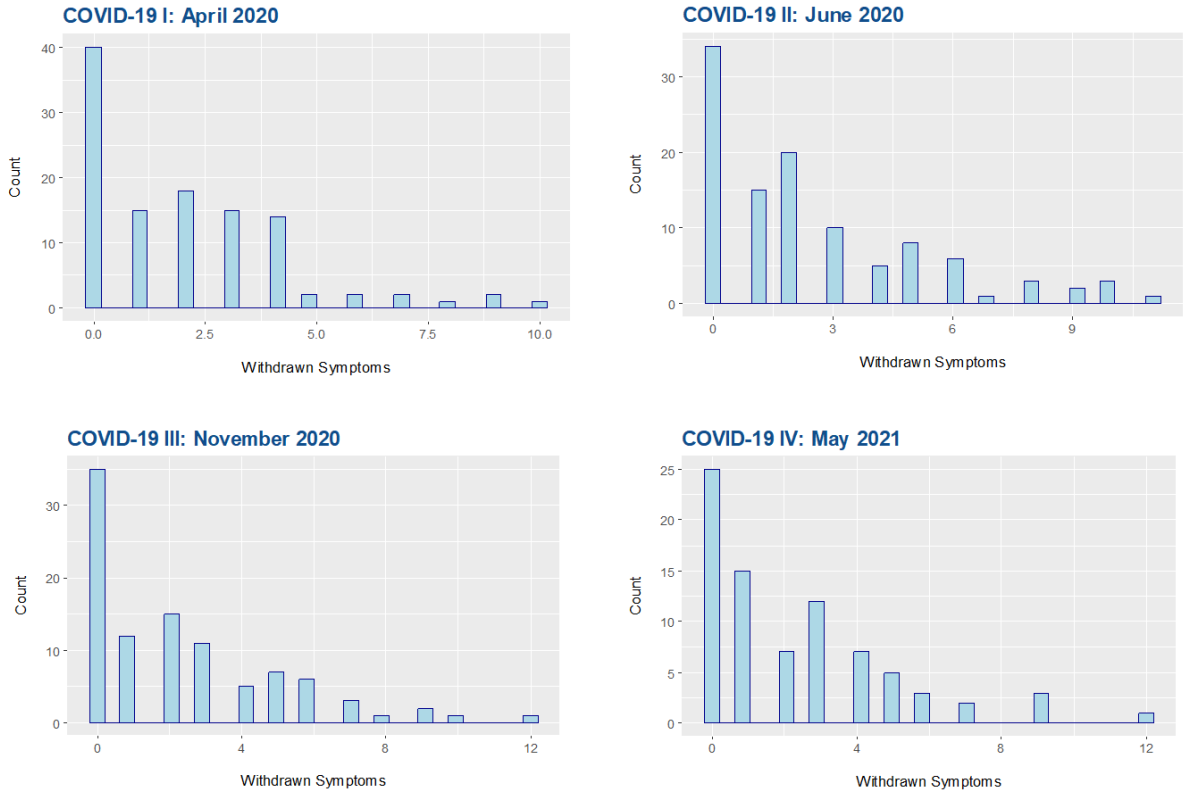

Figure S10. Data distribution for withdrawn symptoms throughout the COVID-19 pandemic.

As depicted in Figure S10, withdrawn symptoms contain a significant number of zeros across the assessments. Due to such high numbers of zeros, the data might not fit standard distributions (e.g., normal distribution) well. To address this, a zero-inflated Poisson (ZIP) model (Lambert, 1992) was chosen, thereby accommodating for zero-inflated data. It combines a logit model to account for the excess zeros and a Poisson regression to model the count data. We here used the ZIP model to handle excessive zeros in withdrawn symptom scale. Neural responses and sex were included in the model as predictors, whereas withdrawn symptoms were included as an outcome variable.

S12. Sensitivity Analyses

The relationship between general cognitive ability and adversity

IQ was negatively associated with the first adversity factor (r=-0.22, p=0.006). There was no significant correlation between IQ and the second and third adversity factors.

To see whether adversity-related neural alterations reflect decreased general cognitive ability, we included IQ (measured at 11 years) in our second-level analyses. These analyses showed that inclusion of IQ in the model did not change the results. As previously, we did not identify neural alterations related to the first and second adversity factor. In this adjusted analysis, significant associations for the third adversity factor were still evident. Higher adversity was related to lower EV signaling in the right putamen (β=-0.23, p=0.004), right NAcc (β=-0.25, p=0.001), and pgACC (β=0.22, p=0.006).Thus, we conclude that decreased general cognitive ability is unlikely to be the driver of the effects.

Interaction Effect of Sex

We conducted additional multiple regression analyses to explore the interaction effect of sex and adversity on neural responses. Regression models with neural responses as the dependent variable were re-examined, incorporating adversity factor (mean-centered), sex, and their interaction terms as predictors. Sex did not predict EV signaling in regions-of-interest. We found a significant interaction between sex and the third adversity factor on activation in the right NAcc (β=-0.26, p=0.001; Figure S11). Specifically, a significant negative correlation between the third adversity factor and EV signaling in the right NAcc was observed only in females (r=-0.31, p=0.003). No other significant interaction effects involving sex were found across the brain regions examined. We did not identify any interaction effect of sex for other regions.

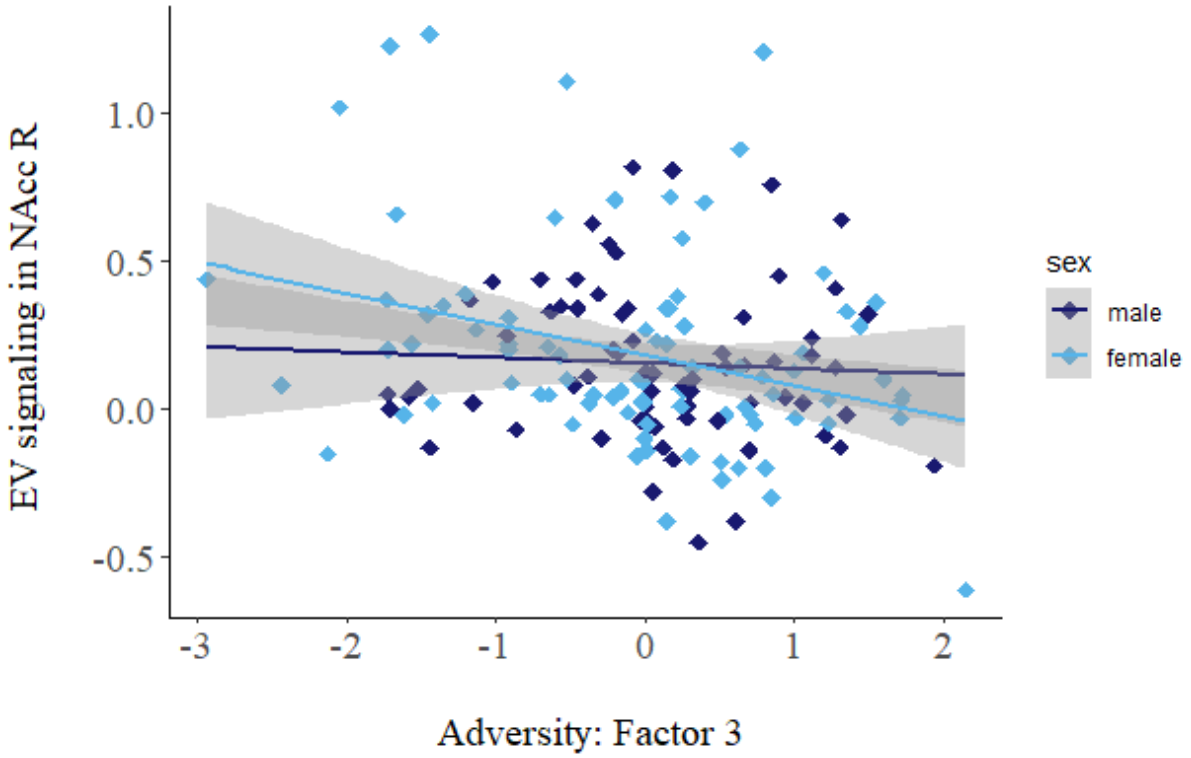

Figure S11. Interaction effect of sex and adversity on neural responses. Associations between the third adversity factor and EV signaling in the right nucleus accumbens were visualized according to sex. Dark blue color represents males, whereas light blue color represents females. Abbreviations: EV, expected value; NAcc, nucleus accumbens.

The Impact of Adversities on Reinforcement Learning in Healthy Participants

The current psychopathology did not predict EV signaling in regions-of-interest. Upon reanalyzing the data excluding the 22 participants with current psychopathology, we observed largely consistent results. As previously, we did not identify neural alterations for the first and second adversity factor. In this adjusted analysis, significant associations for the third adversity factor were still evident (Table S14). Specifically, lower EV signaling in right NAcc, and pgACC remained significant, as did the association between with low maternal stimulation (lower EV signaling in the pgACC). The results for NAcc were replicated when the participants with current

psychopathology were excluded although p values were somewhat higher for right NAcc. However, right putamen results became marginally significant (β=-0.16, p=0.07).

This analysis demonstrates the robustness of our findings within the normative population, albeit with slightly reduced statistical power. The trend-level results for some regions may be attributed to the reduced sample size, as excluding individuals with psychopathology, who are more likely to have experienced adverse events, inevitably impacts the power of our analysis.

Table S14. Multiple regression models for the third adversity factor when participants with current psychopathology were excluded.

Dependent Variable	F3	sex
Caudate L	NS	NS
Caudate R	NS	NS
Putamen L	NS	NS
Putamen R	**-0.16***	NS
NAcc L	NS	NS
NAcc R	**-0.19***	NS
pgACC	**-0.24****	NS
vmPFC	**-0.17***	NS

*p<0.05; **p<0.01; NS: not significant.

Infant Responsiveness

As described in Supplementary Material S2 and our previous work (Holz et al., 2018, 2021), we assessed mother-infant interactions using videotapes of a 10-minute standardized nursing and playing situation between mothers and their 3-month-old babies. Maternal stimulation included all attempts (vocal, facial, and motor) to attract the infant's attention or to establish contact with him/her. Additionally, infant vocal,

facial and motor responsiveness was assessed accordingly to adjust maternal interaction behavior to the infant's behavior. To make sure that our results on the relation between maternal stimulation and EV signaling were not confounded by infant behavior, we conducted several sensitivity analyses. Infant responsiveness was not related to adversity factors or EV signaling in the brain, and the findings remained similar when controlled for infant responsiveness (Table S15).

Table S15. Multiple regression models for maternal stimulation when infant responsiveness was controlled for.

Dependent Variable	Maternal Stimulation	Infant Responsiveness
Caudate L	NS	NS
Caudate R	NS	NS
Putamen L	NS	NS
Putamen R	**0.22****	NS
NAcc L	NS	NS
NAcc R	**0.16***	NS
pgACC	**0.25****	NS
vmPFC	**0.18***	NS

*p<0.05; **p<0.01; NS: not significant.

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7.2 Study II Supplementary Information: Lifespan adversities affect neural correlates of behavioral inhibition in adults

S1. Data Quality Assurance

fMRI data for the stop-signal task was available for 170 participants. Using an extensive quality check procedure, we excluded 49 participants. One participant was excluded due to high motion (> 3 mm in translation or > 3 degrees in rotation). Further three participants were excluded due to signal loss in the frontal cortex (n=1), incidental finding (n=1), and less number of volumes during the fMRI data acquisition (n=1). We also used a consensus guide for the stop-signal task to exclude the participants who did not meet behavioral performance requirements (Verbruggen et al., 2019). One participant was excluded due to poor performance during the go trials (correct go < 80%). Twenty-six participants were excluded since their mean reaction time for unsuccessful stop trials was greater than the mean reaction time for go trials. Finally, we excluded 18 participants who had inhibitory control (i.e., successful stop trials / all stop trials) less than 25% or greater than 75%. The final sample size included 121 participants.

Table S1. Correlations between adversity measures.

	Maternal Stress	Maternal Smoking	Maternal Stimulation	Obstetric Adversity	Family Adversity	Childhood Trauma Questionnaire	Stressful Life Events
Maternal Stress	-	0.09 [b]	-0.04 [b]	**0.20*[b]**	**0.26** [b]**	0.12 [b]	0.15 [b]
Maternal Smoking		-	-0.01 [b]	-0.02 [b]	**0.31*** [b]**	0.15 [b]	**0.40*** [b]**
Maternal Stimulation			-	-0.01 [b]	**-0.29**[a]**	-0.14 [b]	**-0.20*[a]**
Obstetric Adversity				-	-0.09 [b]	-0.02 [b]	-0.01 [b]
Family Adversity					-	**0.33*** [b]**	**0.59*** [a]**
Childhood Trauma Questionnaire						-	**0.41*** [b]**
Stressful Life Events							-

* p < 0.05 ** p < 0.01 *** p < 0.001. a= Pearson's correlation test, b= Spearman's correlation test.

Significant correlations are shown in bold font.

S3. Stop-Signal Task

During the fMRI scan, participants completed a stop-signal task (Rubia et al., 2003), which consisted of two types of trials: Go trials and stop trials. Each trial began with a 500 ms fixation cross. An arrow to the right or left (go-signal) was presented after the fixation cross. During most of the trials (75%), participants were required to respond to the arrow by pressing the right or left button based on the direction of the arrow in the present trial. Infrequently (25%), an upward arrow (stop signal) was presented following the go-signal. The delay between go signal and stop signal started at 250 ms and was adjusted based on participants' performance. If participants correctly inhibited the response, the delay increased by 50 ms (max 900 ms), while it decreased by 50 ms if they failed to inhibit (min 50 ms). The task consisted of 160 trials, which approximately took 7 minutes.

Figure S1. The Stop-Signal Task Design.

S4. MRI Scanning Protocol

Table S2. Structural MRI scanning parameters.

Scanner	TR/TE/T1 (ms)	Flip angle	FOV	Matrix RL/AP/FH	Voxel size (mm)	Acceleration factor
Siemens Magnetom Prisma	1800/2.6/900	8	230	350/263/350	0.9x0.9x0.9	2

Table S3. Functional MRI scanning parameters.

Scanner	TR/TE (ms)	FOV/ Flip angle	Slice number	Slice Order	Voxel Size (mm)	Total Acquisition Time (min)
Siemens Magnetom Prisma	2100/35	192/74	36	Descending	3x3x3	6.37

S5. Principal Component Analysis

Table S4. The rotated component matrix for three-factor solution.

	Factor 1	Factor 2	Factor 3
Maternal Stress	0.26	**0.76**	-0.02
Maternal Smoking	**0.72**	0.04	-0.38
Maternal Stimulation	0.16	0.02	**0.88**
Obstetric Adversity	-0.14	**0.83**	0.03
Family Adversity	**0.80**	0.10	0.13
Childhood Trauma Questionnaire	**0.59**	0.01	0.35
Stressful Life Events	**0.83**	0.02	0.19

S6. Adversity Factors and Psychopathology

The first adversity factor informed by psychosocial adversities and prenatal maternal smoking was associated with higher scores in all psychopathology measures including ADHD (r_s=0.32, p <0.001), anxiety (r_s=0.42, p <0.001), antisocial personality (r_s=0.29, p <0.001), avoidant personality (r_s=0.31, p <0.001), depression (r_s=0.49, p <0.001), and somatic problems (r_s=0.20, p <0.05). All except the latter survived Bonferroni correction. The second adversity factor related to prenatal maternal stress and obstetric adversity was linked to only somatic problems (r_s=-0.22, p <0.05), which did not survive Bonferroni correction. We did not identify any association between psychopathology and the third adversity factor informed by lower maternal stimulation.

S7. FMRI Task Effect

Table S5. Brain regions showing task effect (p< 0.05, FWE-corrected).

Contrast	Direction	Peak Region	Cluster Size	MNI Coordinates			t
StopS vs. Go	Positive	Angular Gyrus L	8393	-45	-61	44	13.12
		MFG L	1192	-39	20	44	11.01
		OFC L	97	-42	35	-13	8.35
		OFC R	13	39	38	-13	6.87
		MFG R	17	42	50	11	6.42
		MFG L	21	-39	50	5	6.31
		PHG L	19	-30	-25	-16	6.15
		ACC R	29	9	35	-7	5.88
	Negative	Insula L	145	-33	21	-1	9.52
		Insula R	149	33	26	-1	9.20
		Midbrain L	74	-3	-31	-1	7.23
		Putamen R	37	18	8	-4	7.04
		Putamen L	45	-18	8	-4	6.69
		IFG R	61	39	8	26	6.52
StopS vs. StopU	Positive	Putamen L	13004	-24	8	-1	16.79
		STG L	132	-57	-7	-4	7.33
		STG R	132	63	-22	-4	7.32
		Cerebellum R	110	42	-67	-34	7.29
		Lingual L	12	-18	-43	-7	5.38
	Negative	Insula L	166	-33	17	-13	9.57
		ACC	359	0	26	26	9.24
		SMA R	70	9	20	65	7.02
		Insula R	43	33	17	-13	6.17

Abbreviations: ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; StopS, stop successful; StopU, stop unsuccessful.

S8. FMRI Task Effect: Post-hoc Analyses

Anatomical Specification of Brain Regions Showing Mixed Activation Pattern

We reported both increased and decreased activation in insula and inferior frontal gyrus for the successful stop versus go trials contrast (See Figure S2A). Anterior insula (Figure S2A, left panel) showed decreased activation during the successful stop trials compared to the go trials. The same activation pattern can also be seen in the contralateral site. These clusters included mostly insula but also inferior frontal gyrus to a smaller extent, posteriorly located in the frontal cortex. In contrast, posterior insula (Figure S2A, middle panel) showed increased activation during the successful stop trials compared to the go trials. Increased activation in the inferior frontal gyrus cluster was anteriorly located and separated from the insula clusters (both anterior and posterior insula clusters; Figure S2A, right panel).

For the successful stop versus unsuccessful stop contrast, we similarly found decreased activation in anterior insula (Figure S2B, left panel). The supplementary motor area showed both increased and decreased activation. Increased activation was located posteriorly (Figure S2B, middle panel), whereas decreased activation was located anteriorly (Figure S2B, right panel).

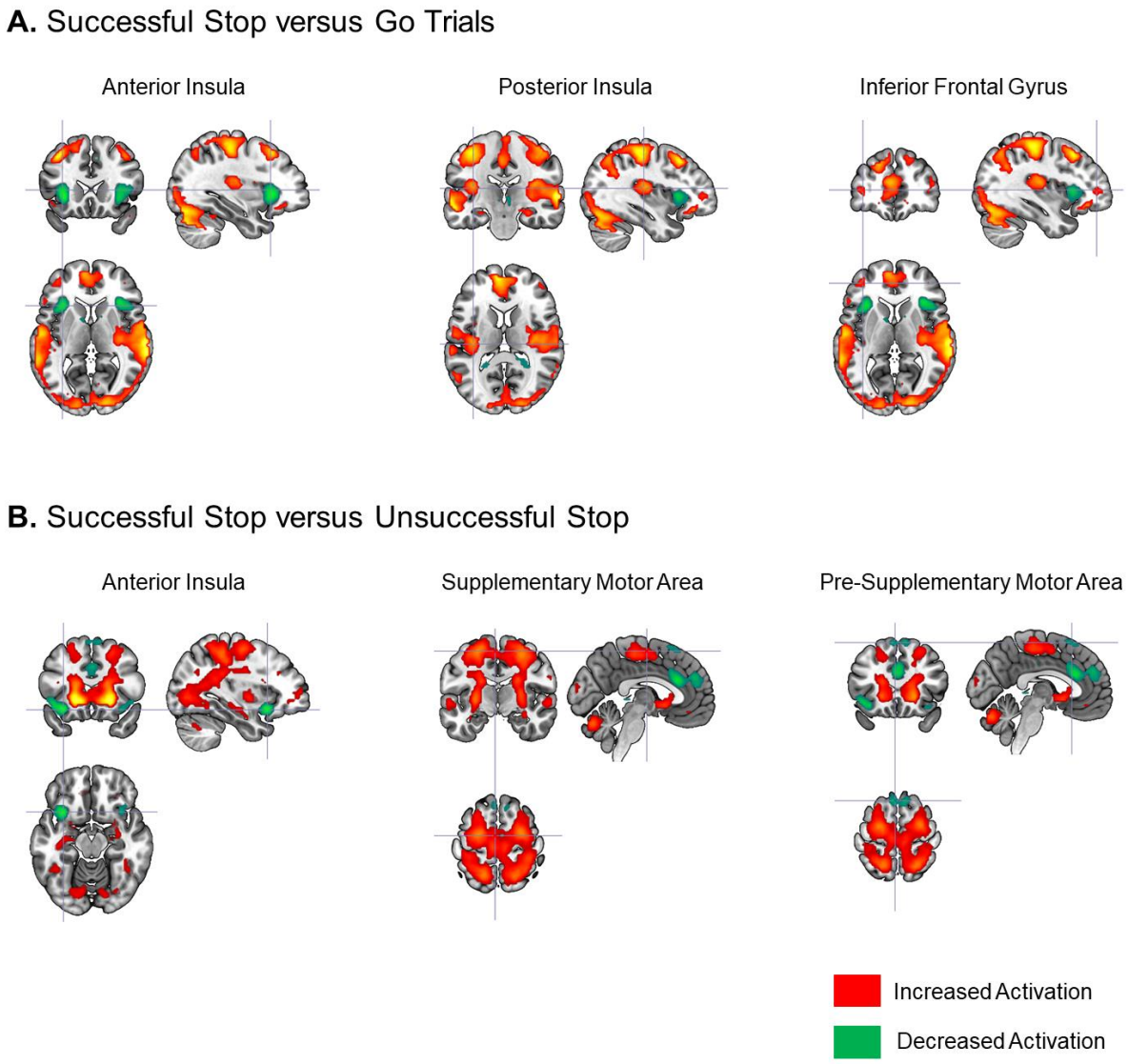

Figure S2. Anatomical specification of brain regions showing both increased and decreased task activation.

Interpretation of Differential Task Effect

Since we identified adversity related brain alteration during successful stop versus unsuccessful stop trials, we wanted to identify brain activation pattern during successful stop > baseline and unsuccessful stop > baseline contrasts to be able to interpret the results for the differential contrast. All results were corrected for family-wise error at whole brain level ($p < 0.05$).

During successful stop trials compared to baseline, we found enhanced activation in cerebellum, occipital cortex, precentral and postcentral gyri, supplementary motor area, inferior parietal cortex, several temporal regions (middle temporal gyrus, superior temporal gyrus), middle and superior frontal gyri, insula, and striatum. At uncorrected level, we also identified increased activation in the inferior frontal gyri, especially in the left hemisphere. We also found decreased activation in insula, lingual gyrus, fusiform, parahippocampal gyrus, cuneus, precuneus, brainstem, and right inferior frontal gyrus (Figure S3).

During unsuccessful stop trials compared to baseline, we found enhanced activation in dorsal anterior cingulate cortex, superior medial frontal cortex, supplementary motor area, middle temporal gyrus, insula, fusiform gyrus, and left inferior frontal gyrus. We also identified decreased activation in middle temporal gyrus, occipital cortex, striatum, insula, inferior frontal gyrus, precuneus, postcentral gyrus, and middle and superior frontal gyri.

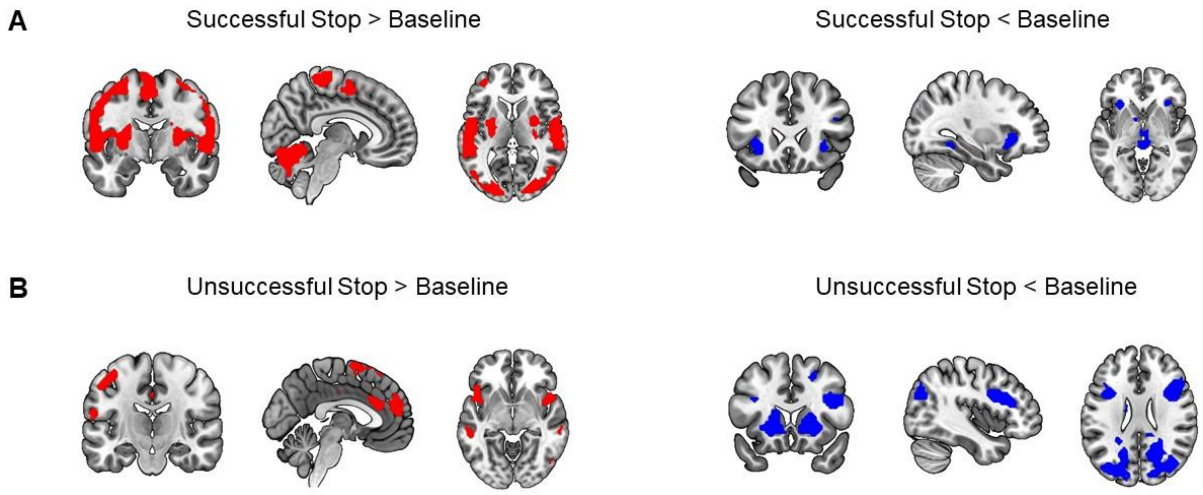

Figure S3. Brain activation during successful stop trials versus baseline (A) and unsuccessful stop trials versus baseline (B). All results were corrected for family-wise error ($p < 0.05$).

Overlap between Adversity and Task Effects

In terms of adversity and task effect overlap, we found that adversity-related middle temporal gyrus and insula activation were present in both successful and unsuccessful trials compared to baseline (Figure S4). However, the overlap between the adversity and task effect in bilateral MTG was more apparent in the successful stop trials compared to baseline, whereas the overlap between the adversity and task effect in left insula was more apparent in the unsuccessful stop trials compared to baseline. Right insula showed comparable overlap during the both conditions compared to baseline, although it was more activated in the unsuccessful stop trials compared to successful stop trials (Figure S5). Adversity related dACC/superior medial prefrontal cortex activation overlapped only with the task effect during unsuccessful stop trials compared to baseline. No dACC activation was found during successful stop trials versus baseline. Adversity related IFG activation did not overlap with any of the task contrast.

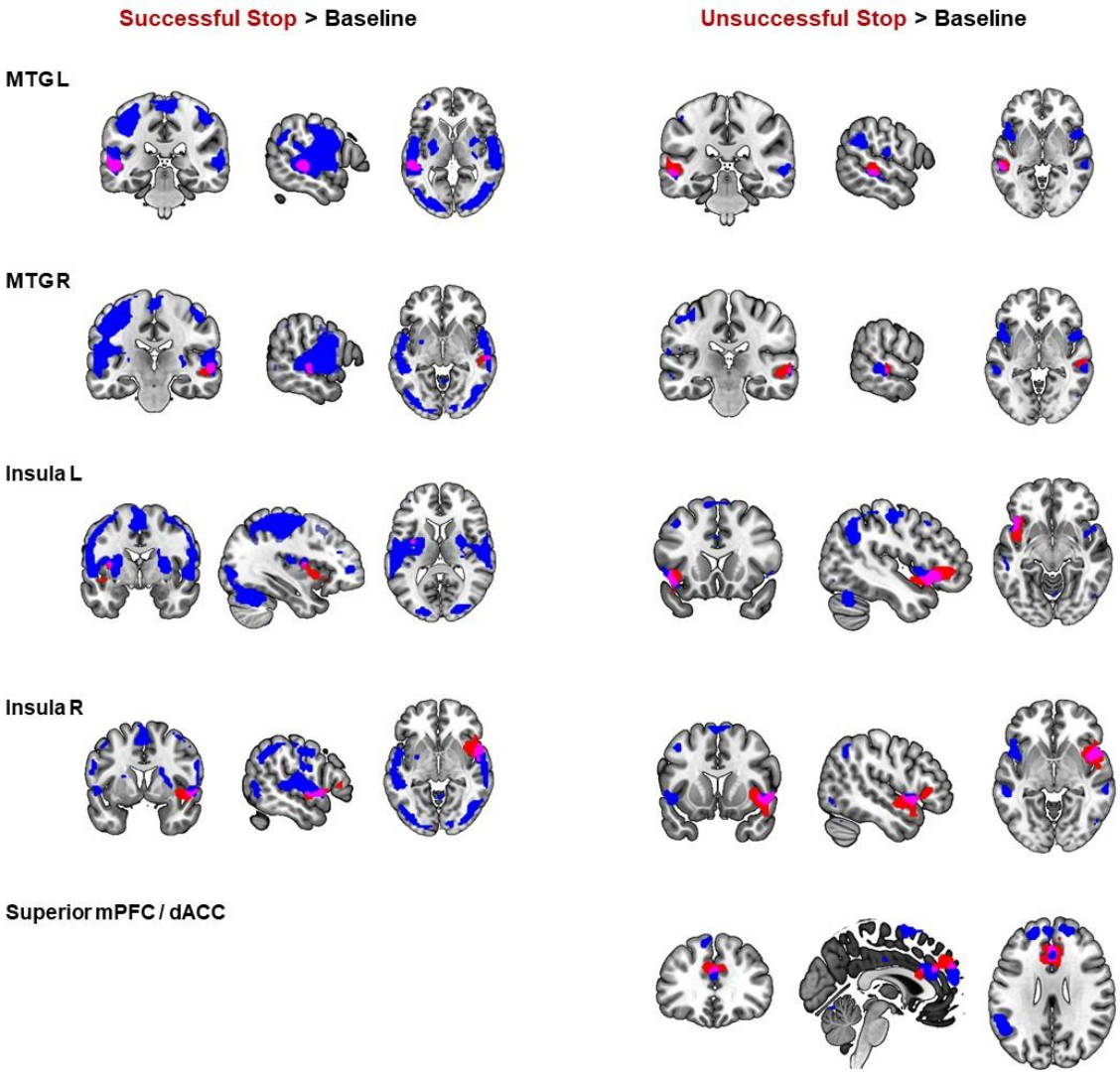

Figure S4. Overlap between the adversity effect and task effect during successful stop trials versus baseline (left panel) and unsuccessful stop trails versus baseline (right panel). Blue, red, and pink colors represents task effect, adversity effect, and the overlap between them respectively.

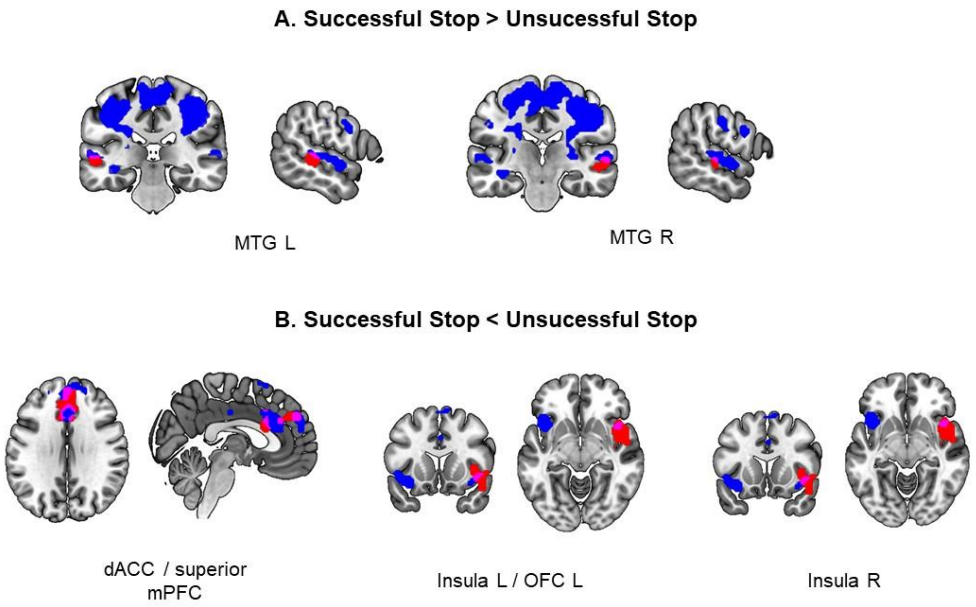

Figure S5. Overlap between the adversity effect and task effect during successful stop trials versus unsuccessful stop trails. Blue, red, and pink colors represents task effect, adversity effect, and the overlap between them respectively.

S9. Brain-Behavior Relationship

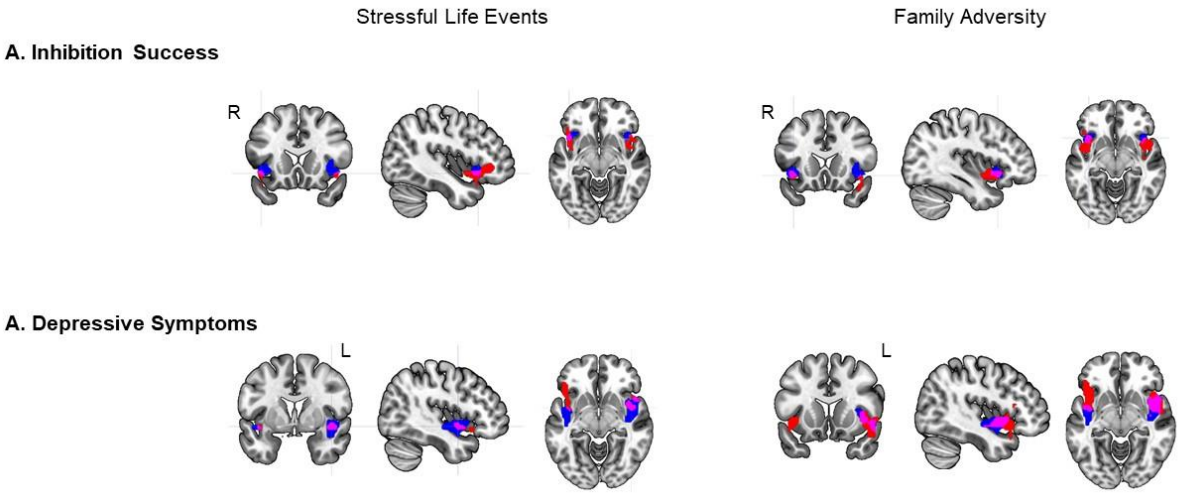

Figure 6. The overlap between specific adversities and behavior in bilateral insula. Blue, red, and pink colors represents behavior, adversity effect, and the overlap between them respectively.

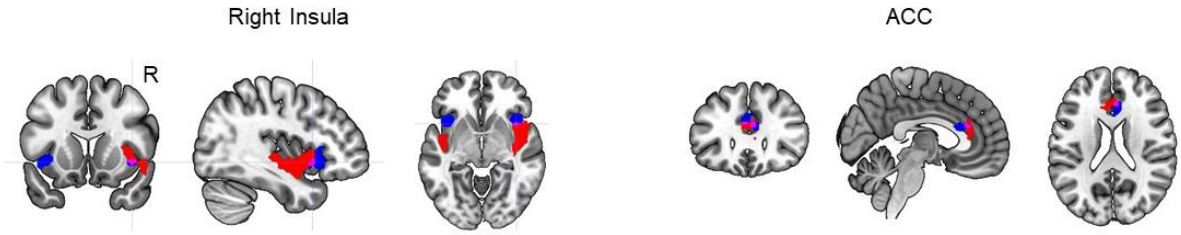

Figure 7. The overlap between inhibition success and depressive symptoms during successful versus unsuccessful stop trials. Blue, red, and pink colors represents inhibition success, depressive symptoms, and the overlap between them respectively.

S10. Neural Correlates of Stop Signal Reaction Time

We conducted a regression analysis in SPM 12 using the stop signal reaction time (SSRT) scores for the successful versus unsuccessful stop trials contrast in which we identified adversity effect. The results are shown in the Figure S8. Higher scores in SSRT was associated with higher activation in several default-mode network regions including left angular gyrus extending middle occipital gyrus (T=5.71, k=296), right angular gyrus (T=5.00, k=105), posterior cingulate cortex /precuneus (T=5.28, k=358) and medial orbitofrontal cortex (T=4.39, k=71) during successful versus unsuccessful stop trials ($p < 0.001$ for cluster-forming threshold, $p < 0.05$, cluster-level FWE corrected). On the other hand, higher scores in SSRT was associated with lower activation in right insula and inferior frontal gyrus (T=4.89, k=91) during successful versus unsuccessful stop trials ($p < 0.001$ for cluster-forming threshold, $p < 0.05$, cluster-level FWE corrected).

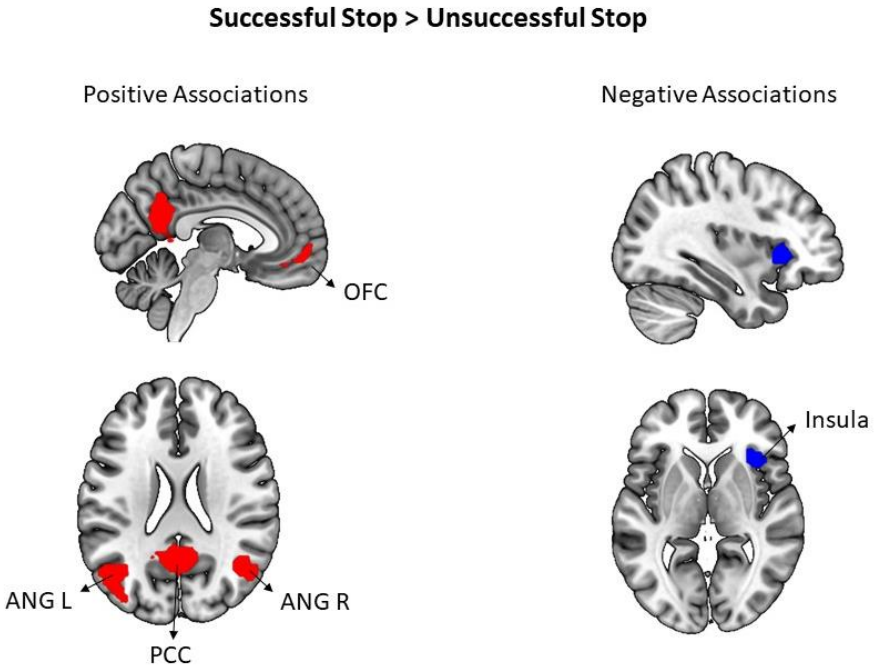

Figure S8. Neural correlates of stop signal reaction time during successful versus unsuccessful stop trials. Abbreviations: ANG, angular gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex.

S11. Timing Effect of Adversities

Family adversity and stressful life events were assessed at multiple time points across development. We measured family adversity from 3 months (T1) to 11 years (T5) across five assessment waves. It included 11 adverse family factors (e.g., parental psychopathology, marital discord, poor coping skills of parents etc.) at T1. Two items were excluded (unwanted pregnancy and early parenthood) at the following assessment waves since they were specific to T1 measurement. We measured stressful life events, the presence of several life stressors in different domains (partnership, work, health etc.), using the adapted version of the Munich Event List (Maier-Diewald et al., 1983) across 11 assessment waves. We calculated Z-transformed scores for each time point and used these time-specific sum scores for the current analysis.

To examine if there is a time window of increased vulnerability to family adversity and stressful life events in the context of inhibitory control, we conducted several regression analyses. All analyses were controlled for sex and current psychopathology. P was set to 0.001 to identify clusters at whole-brain and the identified clusters were reported if $p < 0.05$ family-wise error corrected at cluster level.

There were significant strong positive correlations between family adversity measures at different time points (Table S6), whereas stressful life events showed small to moderate positive correlations between time points (Table S7).

During successful versus unsuccessful stop trials, family adversity was associated with higher activation in brainstem at T1 (3 months), higher activation in bilateral insula at T2 (2 years) and T3 (4.5 years) and higher activation in left insula at T4 (8 years) and T5 (11 years) (all $p < 0.05$ FWE-corrected at cluster level; Table S8 and Figure S9). Stressful life events were linked to higher activation in MTG at T2,

higher activation in left insula\IFG activation at T5, higher activation in dACC, pregenual ACC, middle cingulum, left caudate, and left angular gyrus at T7 (19 years), and higher activation in dACC and middle cingulum at T9 (23 years) during successful versus unsuccessful stop trials (all $p < 0.05$ FWE-corrected at cluster level; Table S9 and Figure S9).

Table S6. The Spearman's correlations between family adversity measures.

	T1	T2	T3	T4	T5
T1	-	.69***	.63***	.59***	.52***
T2		-	.71***	.55***	.52***
T3			-	.65***	.57***
T4				-	.75***
T5					-

*** $p < 0.001$

Table S7. The Pearson's correlations between stressful life events measures.

	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11
T1	-	.50***	.41***	.23*	.32****	.28***	.22*	.32***	.18*	.18*	.06
T2		-	.53***	.34***	.22*	.21*	.26**	.26**	.21*	.16	.25**
T3			-	.44***	.18*	.16	.16	.26**	.26**	.17	.19*
T4				-	.38***	.31**	.13	.14	.22*	.10	.04
T5					-	.41***	.44***	.24*	.21*	.04	.10
T6						-	.27**	.03	.02	.13	-.06
T7							-	.42***	.48***	.19*	.25**
T8								-	.51***	.37***	.40***
T9									-	.29**	.34***
T10										-	.38***
T11											-

*p <0.05 **p<0.01 ***p<0.001

Table S8. Timing effect of family adversity on brain responses during inhibitory control (successful versus unsuccessful stop trials)

Time	Region	k	t	MNI coordinates [x y z]		
T1	Brainstem	72	4.06	-9	-37	-22
T2	Insula L	112	5.16	-42	5	-10
	Insula R	77	4.44	48	11	-10
T3	Insula L	112	5.29	-39	8	-7
	Insula R	97	5.02	42	11	-7
T4	Insula L	70	5.95	-42	5	-10
T5	Insula L	86	4.83	-39	8	-7

$p < 0.05$ (FWE-corrected at cluster level).

Table S9. Timing effect of stressful life events on brain responses during inhibitory control (successful versus unsuccessful stop trials)

Time	Region	k	t	MNI coordinates [x y z]		
T2	MTG L	89	5.19	-54	-31	-1
T5	Insula L	75	4.18	-45	26	-4
T7	pgACC	96	5.01	-9	41	14
	dACC	360	4.96	-6	38	38
	ANG L	120	4.34	-39	-73	41
	MCC	103	4.27	-6	-34	35
	Caudate L	121	4.20	-12	14	2
T9	dACC	81	4.24	-9	32	29
	MCC	98	3.86	9	-46	38

$p < 0.05$ (FWE-corrected at cluster level). Abbreviations: ANG, angular gyrus; dACC, dorsal anterior cingulate cortex; MCC, middle cingulate cortex; pgACC, pregenual anterior cingulate cortex.

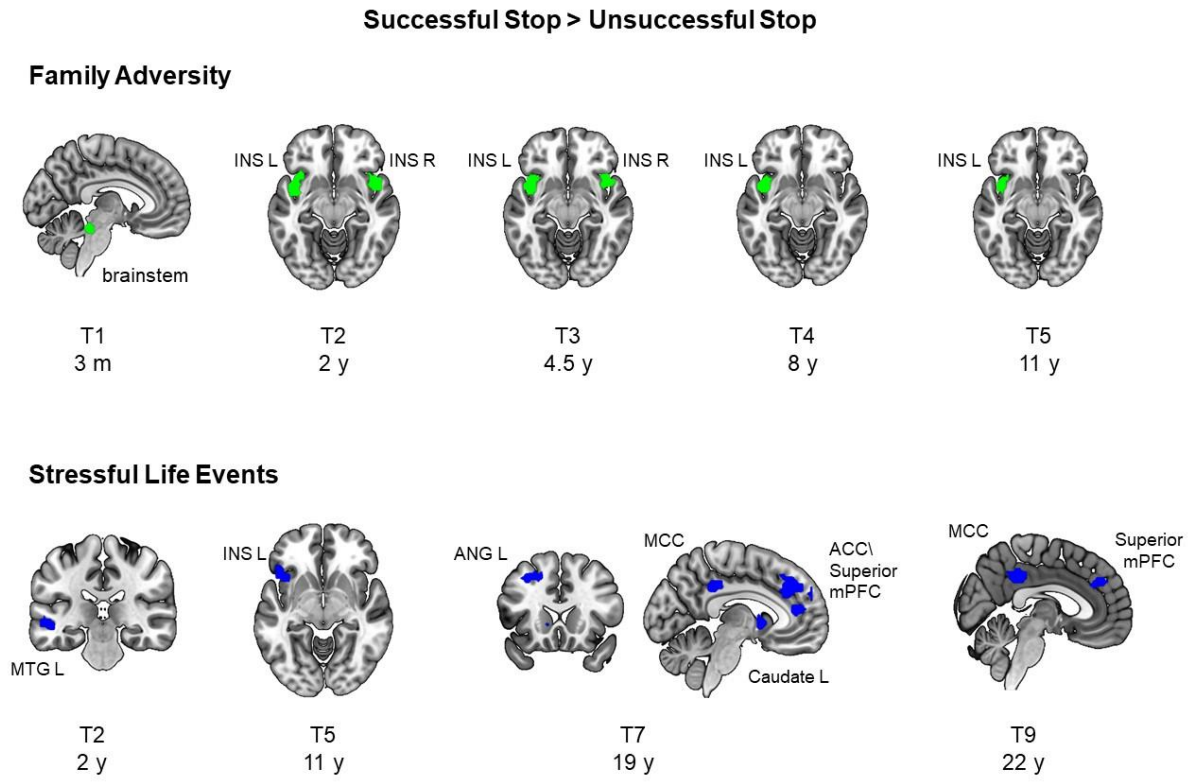

Figure S9. Timing effect of prospectively collected adversities on brain responses during successful versus unsuccessful stop trials ($p < 0.05$, FWE corrected at cluster level). Abbreviations: ACC, anterior cingulate cortex; ANG, angular gyrus; INS, insula; MCC, middle cingulate cortex; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus.

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7.3 Study III Supplementary Information: The long-term correlates of developmental stress on whole-brain functional connectivity during emotion regulation

S1. Study Design

Mannheim Study of Children at Risk is a longitudinal birth cohort study designed to investigate long-term outcomes of early psychosocial and biological risk factors on development (Laucht et al., 2000). The initial sample included 384 children born between 1986 and 1988. The participants were followed from their birth up to the age of 33 years across 11 assessment waves. Across the assessment waves, several measures of adversity, psychopathology, and socio-emotional behavior were collected alongside biological, neurophysiological, and neuroimaging data. Figure S1 illustrates only the assessments used for the current study.

At the last assessment wave, 256 (67%) participants agreed to participate in the study. Among them, 170 participants completed several task-based fMRI paradigms in social and emotional domains.

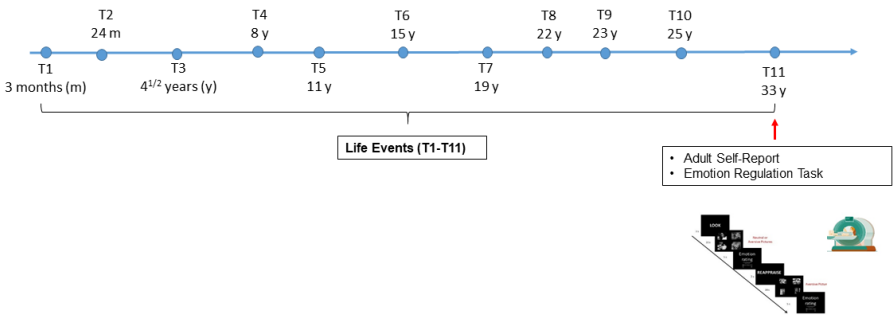

Figure S1. Design of Mannheim Study of Children at Risk.

S2. Stressful Life Events

Stressful life events were measured using a modified version of the Munich Event List (Maier-Diewald et al., 1983). The items covered positive and negative stressors in several domains, including partnership, education, work, health, and finance. At the first assessment wave, parents were asked to report occurrence of life events in the last year, which covered prenatal and newborn period. From T2 on, life events were noted if they occurred between the previous assessment wave and the current assessment wave. Between T1 and T6 (15 years), trained psychologists conducted a standardized interview with caregivers. The caregiver reported occurrence and frequency of each event. Starting at the 15-year assessment, participants rated stressful life events themselves. However, since the adolescent version at T6 was a short version and did not cover all domains, we opted to use the parent version for compatibility. At T7, only occurrence is counted, no information regarding frequency was collected. T11 measure covered the events that occurred in the last 12 months.

Table S1. Stressful Life Events.

	T1	T2	T3	T4	T5	T6	T7	T11
Item number	41	42	44	47	47	50	53	57
Mean (SD)	3.80(2.49)	5.58(3.20)	6.63(3.35)	6.72(3.54)	5.57(3.40)	6.37(3.73)	7.22(4.55)	4.07(3.45)
Score range	1-15	0-21	2-17	0-23	0-16	0-22	0-28	0-18

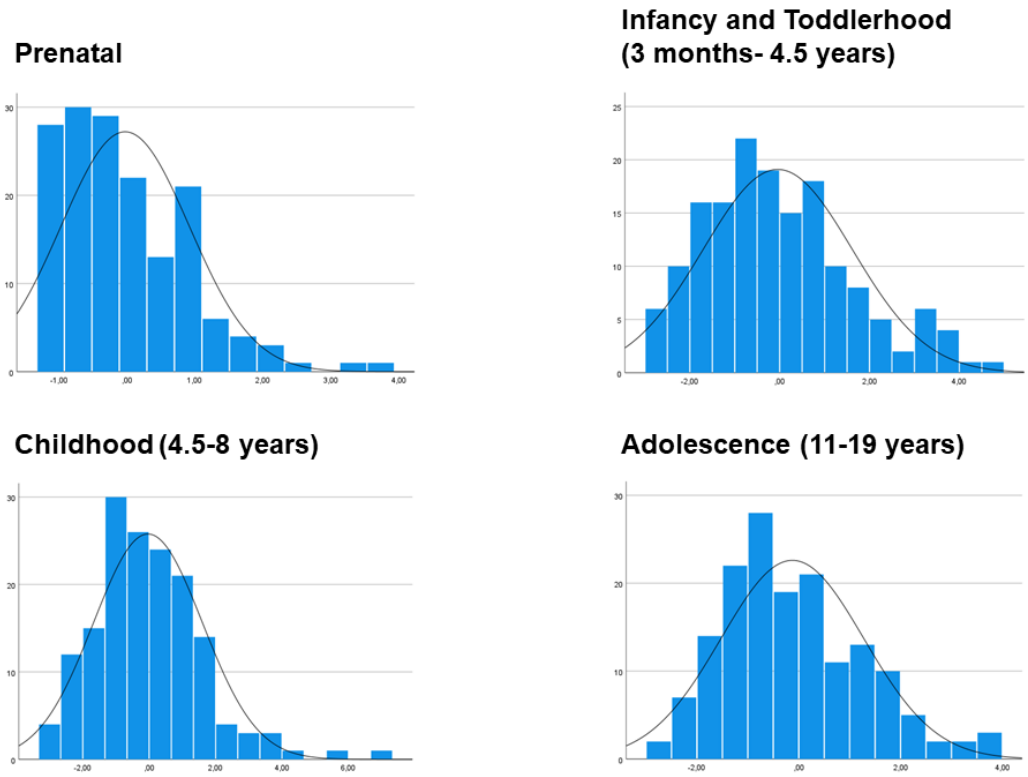

Figure S2. Data Distribution.

Table S2. Spearman's correlation between life stress variables.

	Prenatal	Infancy/ Toddlerhood	Childhood	Adolescence	Current (T11)
Prenatal	-	0.42**	0.30**	0.26*	0.07
Infancy/ Toddlerhood		-	0.43**	0.30**	0.15
Childhood			-	0.45**	0.06
Adolescence				-	0.08
Current (T11)					-

*p<0.01 **p< 0.001

S3. Experimental Paradigm

Each block started with a 3 s instruction (e.g., Look or Reappraise). Participants subsequently viewed a 20 s block of neutral or negative images from the International Affective Picture System (Lang et al., 2008). Each image was presented for 5 s consecutively without an interstimulus interval. Immediately following the experimental block, participants were asked to rate the intensity of their negative affect on a 7-point Likert scale (1 = no negative feelings at all; 7 = extremely negative feelings) via a button press (max 4 s). 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 randomly presented in four runs with a maximum of two presentations of the same condition in succession.

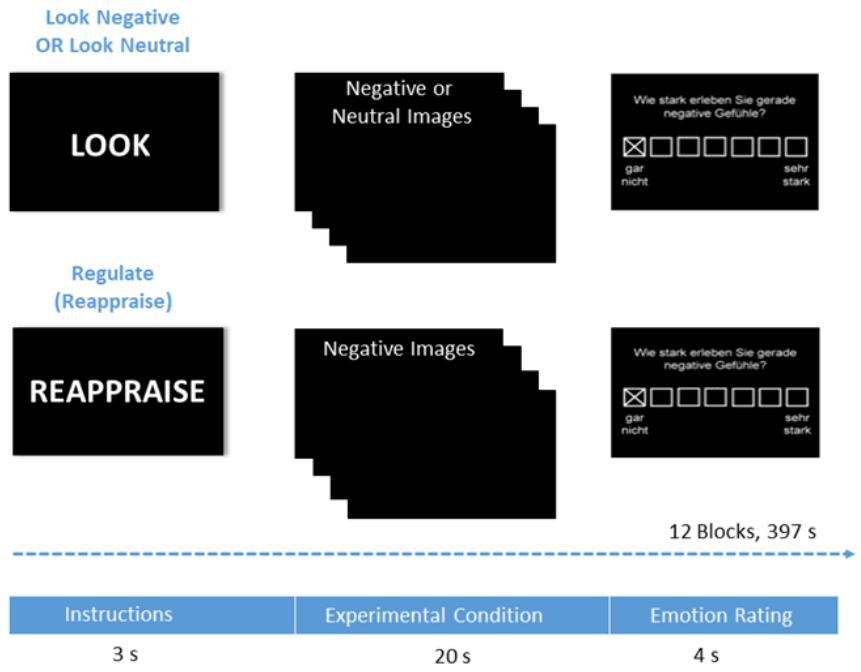

Figure S3. Emotion Regulation Task.

S4. Brain-Behavior Relationship

Simple linear regression using the ordinary least square approach was conducted to see if altered connectivity was linked to any psychopathology measure (internalizing or externalizing symptoms). The test is conducted for 236, 41, and 5 connection parameters related to prenatal, childhood and adolescence stress respectively. Connections parameter showing a significant association (FDR-$p < 0.05$) was reported in the Table S7 with their coefficients and adjusted R^2 scores.

S5.Task-Related Brain Activation

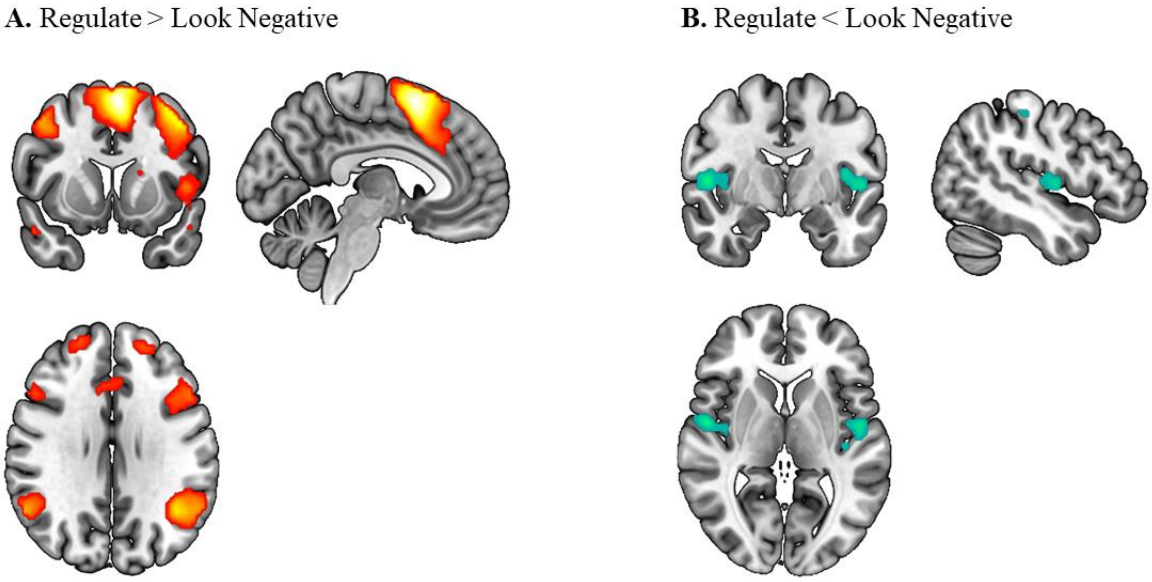

Figure S4. Task-related activation during emotion regulation task. (A) Brain regions showing increased activation during the emotion regulation condition compared to the look negative condition were mapped on brain surface in hot colors using MRIcroGL (https://www.nitrc.org/projects/mricrogl). (B) Brain regions showing decreased activation during the emotion regulation condition compared to the look negative condition were mapped on brain surface in cold colors. $P < 0.05$ (FWE-corrected).

S6. Developmental Stress and Task-Related Brain Activation

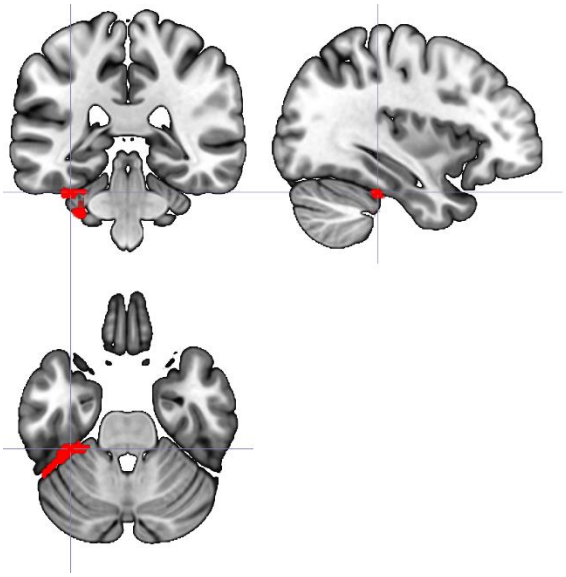

Figure S5. The association between childhood stress and brain activation during emotion regulation. Cluster depicted with the red color included left fusiform and cerebellum (k=83, t=4.52, $p < 0.05$ cluster-level FWE corrected).

S7. Task-Dependent Functional Connectivity

Table S3. Task-dependent functional connectivity during emotion regulation (Network-Based Statistic (NBS)-corrected).

Connection	Seed Name	Target Name	Seed Network	Target Network	t	Hedge's g
1	SFG_R_7_1	SFG_L_7_1	SN	FPN	-3.98	-0.31
2	SFG_L_7_4	SFG_L_7_1	DAN	FPN	-3.8	-0.3
3	MFG_L_7_4	SFG_L_7_1	FPN	FPN	-3.56	-0.28
4	IFG_L_6_5	SFG_L_7_1	SN	FPN	-3.63	-0.28
5	IFG_L_6_6	SFG_L_7_1	SN	FPN	-4.24	-0.33
6	pSTS_L_2_1	SFG_L_7_1	DMN	FPN	-3.59	-0.28
7	SPL_L_5_3	SFG_L_7_1	DAN	FPN	-3.97	-0.31
8	IPL_R_6_3	SFG_L_7_1	DAN	FPN	-4.05	-0.32
9	PCun_L_4_1	SFG_L_7_1	FPN	FPN	-4.06	-0.32
10	PCun_R_4_1	SFG_L_7_1	FPN	FPN	-3.91	-0.31
11	MVOcC _R_5_2	SFG_L_7_1	VIS	FPN	-4.33	-0.34
12	MFG_L_7_2	SFG_R_7_1	FPN	SN	-3.62	-0.28
13	IFG_L_6_3	SFG_R_7_1	DMN	SN	-3.74	-0.29
14	IFG_L_6_5	SFG_R_7_1	SN	SN	-3.86	-0.3
15	IFG_L_6_6	SFG_R_7_1	SN	SN	-4.28	-0.34
16	IFG_R_6_4	SFG_R_7_4	FPN	DAN	-3.58	-0.28
17	IFG_L_6_3	SFG_L_7_5	DMN	SMN	-3.52	-0.28
18	IFG_L_6_6	SFG_L_7_5	SN	SMN	-4.33	-0.34
19	SPL_L_5_4	SFG_L_7_5	SMN	SMN	-3.91	-0.31
20	PCun_L_4_2	SFG_L_7_5	SMN	SMN	-3.55	-0.28
21	INS_R_6_6	SFG_L_7_5	SN	SMN	-3.56	-0.28
22	CG_R_7_5	SFG_L_7_5	SN	SMN	-3.81	-0.3
23	IFG_L_6_6	SFG_R_7_5	SN	SMN	-3.52	-0.28
24	SPL_L_5_4	SFG_R_7_5	SMN	SMN	-3.92	-0.31
25	CG_R_7_5	SFG_R_7_5	SN	SMN	-3.85	-0.3
26	SFG_L_7_6	SFG_R_7_6	DMN	FPN	-3.52	-0.28
27	SFG_L_7_2	MFG_L_7_1	DMN	SN	-3.52	-0.28
28	IFG_L_6_3	MFG_L_7_1	DMN	SN	-3.54	-0.28
29	IFG_R_6_4	MFG_R_7_1	FPN	FPN	-3.64	-0.29
30	pSTS_R_2_1	MFG_L_7_6	DMN	DAN	-3.66	-0.29
31	SPL_L_5_5	IFG_L_6_1	DAN	FPN	-3.94	-0.31
32	SPL_R_5_5	IFG_L_6_1	DAN	FPN	-3.76	-0.29
33	PCun_L_4_1	IFG_L_6_1	FPN	FPN	-3.6	-0.28
34	PCun_R_4_1	IFG_L_6_1	FPN	FPN	-3.57	-0.28
35	PCun_L_4_3	IFG_L_6_1	VIS	FPN	-3.59	-0.28
36	PCun_R_4_3	IFG_L_6_1	VIS	FPN	-4.37	-0.34
37	MVOcC _R_5_2	IFG_L_6_1	VIS	FPN	-3.76	-0.3
38	SFG_R_7_1	IFG_L_6_5	SN	SN	-3.69	-0.29
39	IFG_L_6_3	IFG_L_6_5	DMN	SN	-3.84	-0.3
40	OrG_R_6_6	IFG_L_6_5	DMN	SN	-3.62	-0.28
41	INS_L_6_3	IFG_L_6_5	SN	SN	-4.56	-0.36

42	INS_R_6_3	IFG_L_6_5	SN	SN	-3.81	-0.3
43	MVOcC _R_5_3	IFG_R_6_5	VIS	SN	-3.58	-0.28
44	IFG_R_6_5	IFG_L_6_6	SN	SN	-4.12	-0.32
45	INS_L_6_3	IFG_L_6_6	SN	SN	-4.15	-0.33
46	INS_R_6_3	IFG_L_6_6	SN	SN	-4.43	-0.35
47	MVOcC _L_5_3	OrG_R_6_1	VIS	DMN	-3.84	-0.3
48	IFG_L_6_3	PrG_L_6_2	DMN	DAN	-3.77	-0.3
49	IFG_R_6_4	PrG_L_6_2	FPN	DAN	-3.76	-0.3
50	SFG_L_7_5	PrG_R_6_5	SMN	SN	-3.94	-0.31
51	SFG_R_7_5	PrG_R_6_5	SMN	SN	-3.54	-0.28
52	STG_R_6_3	PrG_R_6_5	SMN	SN	-3.53	-0.28
53	IPL_L_6_6	PrG_R_6_5	SMN	SN	-3.61	-0.28
54	INS_L_6_6	PrG_R_6_5	SN	SN	-3.74	-0.29
55	INS_R_6_6	PrG_R_6_5	SN	SN	-3.57	-0.28
56	CG_L_7_5	PrG_R_6_5	SN	SN	-4.02	-0.32
57	CG_R_7_5	PrG_R_6_5	SN	SN	-3.8	-0.3
58	pSTS_R_2_2	PrG_L_6_6	SN	DAN	-3.53	-0.28
59	SPL_L_5_1	PrG_L_6_6	DAN	DAN	-3.86	-0.3
60	SPL_L_5_5	PrG_L_6_6	DAN	DAN	-3.65	-0.29
61	PCun_R_4_3	PrG_L_6_6	VIS	DAN	-3.69	-0.29
62	MVOcC _R_5_2	PrG_L_6_6	VIS	DAN	-3.82	-0.3
63	CG_R_7_6	STG_L_6_2	SN	SMN	-3.75	-0.29
64	LOcC_L_4_3	MTG_L_4_4	VIS	DMN	-3.94	-0.31
65	MVOcC _L_5_3	FuG_L_3_2	VIS	VIS	-3.6	-0.28
66	PrG_L_6_4	FuG_R_3_2	SMN	VIS	-3.59	-0.28
67	SPL_L_5_5	FuG_R_3_2	DAN	VIS	-3.73	-0.29
68	PoG_L_4_3	FuG_R_3_2	DAN	VIS	-3.65	-0.29
69	MVOcC _L_5_1	FuG_R_3_2	VIS	VIS	-4.59	-0.36
70	MVOcC _L_5_2	FuG_R_3_2	VIS	VIS	-4.31	-0.34
71	MVOcC _L_5_3	FuG_R_3_2	VIS	VIS	-4.48	-0.35
72	MVOcC _L_5_1	FuG_L_3_3	VIS	DAN	-3.62	-0.28
73	MVOcC _L_5_3	FuG_L_3_3	VIS	DAN	-3.7	-0.29
74	MVOcC _L_5_1	FuG_R_3_3	VIS	VIS	-4.29	-0.34
75	MVOcC _L_5_3	FuG_R_3_3	VIS	VIS	-3.65	-0.29
76	SPL_L_5_5	pSTS_L_2_1	DAN	DMN	-3.77	-0.3
77	MVOcC _R_5_5	pSTS_R_2_2	VIS	SN	-3.61	-0.28
78	IFG_L_6_3	SPL_L_5_2	DMN	DAN	-3.68	-0.29
79	IFG_L_6_6	SPL_L_5_2	SN	DAN	-3.63	-0.28
80	IFG_L_6_3	SPL_R_5_2	DMN	DAN	-3.89	-0.31
81	IFG_R_6_4	SPL_R_5_2	FPN	DAN	-3.56	-0.28
82	IFG_L_6_2	SPL_L_5_5	FPN	DAN	-3.66	-0.29
83	IFG_L_6_3	SPL_L_5_5	DMN	DAN	-3.85	-0.3
84	IFG_L_6_2	SPL_R_5_5	FPN	DAN	-3.55	-0.28
85	IFG_L_6_3	SPL_R_5_5	DMN	DAN	-3.87	-0.3
86	IFG_R_6_4	IPL_L_6_3	FPN	DAN	-3.54	-0.28
87	IFG_L_6_2	IPL_R_6_3	FPN	DAN	-3.5	-0.27
88	IFG_L_6_3	IPL_R_6_3	DMN	DAN	-3.61	-0.28

89	IFG_R_6_4	IPL_R_6_4	FPN	FPN	-3.84	-0.3
90	CG_R_7_6	IPL_L_6_6	SN	SMN	-3.62	-0.28
91	SFG_L_7_5	IPL_R_6_6	SMN	SMN	-3.69	-0.29
92	SFG_R_7_5	IPL_R_6_6	SMN	SMN	-3.66	-0.29
93	INS_L_6_6	IPL_R_6_6	SN	SMN	-3.55	-0.28
94	CG_R_7_5	IPL_R_6_6	SN	SMN	-3.66	-0.29
95	CG_L_7_6	IPL_R_6_6	SN	SMN	-3.65	-0.29
96	IFG_L_6_3	PCun_L_4_1	DMN	FPN	-3.73	-0.29
97	IFG_L_6_3	PCun_R_4_1	DMN	FPN	-4.18	-0.33
98	IFG_R_6_4	PCun_R_4_1	FPN	FPN	-3.87	-0.3
99	IFG_L_6_6	PCun_R_4_1	SN	FPN	-3.61	-0.28
100	MFG_L_7_2	PCun_L_4_3	FPN	VIS	-3.85	-0.3
101	IFG_L_6_3	PCun_L_4_3	DMN	VIS	-4.65	-0.36
102	IFG_R_6_4	PCun_L_4_3	FPN	VIS	-3.6	-0.28
103	IFG_L_6_6	PCun_L_4_3	SN	VIS	-4.27	-0.33
104	MFG_L_7_2	PCun_R_4_3	FPN	VIS	-3.51	-0.28
105	IFG_L_6_3	PCun_R_4_3	DMN	VIS	-4.73	-0.37
106	IFG_R_6_4	PCun_R_4_3	FPN	VIS	-3.76	-0.29
107	IFG_L_6_6	PCun_R_4_3	SN	VIS	-3.75	-0.29
108	pSTS_R_2_1	PCun_R_4_3	DMN	VIS	-4.2	-0.33
109	IFG_L_6_3	PoG_L_4_1	DMN	SMN	-3.75	-0.29
110	pSTS_L_2_2	PoG_L_4_1	SN	SMN	-3.58	-0.28
111	IFG_R_6_4	PoG_L_4_3	FPN	DAN	-3.5	-0.27
112	SPL_L_5_4	INS_L_6_1	SMN	SMN	-3.79	-0.3
113	BG_L_6_4	INS_R_6_1	SUB	SMN	-3.76	-0.3
114	IFG_L_6_2	INS_L_6_5	FPN	SMN	-3.51	-0.28
115	SFG_L_7_5	INS_L_6_6	SMN	SN	-3.59	-0.28
116	SFG_R_7_5	INS_L_6_6	SMN	SN	-3.75	-0.29
117	IFG_L_6_3	INS_L_6_6	DMN	SN	-3.9	-0.31
118	INS_R_6_6	INS_L_6_6	SN	SN	-3.99	-0.31
119	CG_R_7_5	INS_L_6_6	SN	SN	-3.73	-0.29
120	LOcC_L_4_3	CG_L_7_2	VIS	SUB	-3.55	-0.28
121	SFG_L_7_2	CG_L_7_3	DMN	DMN	-3.84	-0.3
122	SFG_L_7_6	CG_L_7_3	DMN	DMN	-3.75	-0.29
123	PCun_L_4_2	CG_L_7_3	SMN	DMN	-3.87	-0.3
124	MVOcC _R_5_2	CG_L_7_3	VIS	DMN	-3.64	-0.29
125	SFG_L_7_1	CG_R_7_3	FPN	SN	-4.29	-0.34
126	SFG_L_7_4	CG_R_7_3	DAN	SN	-3.72	-0.29
127	SFG_L_7_6	CG_R_7_3	DMN	SN	-3.53	-0.28
128	MFG_L_7_1	CG_R_7_3	SN	SN	-3.51	-0.28
129	IFG_L_6_3	CG_R_7_3	DMN	SN	-3.83	-0.3
130	IFG_R_6_4	CG_R_7_3	FPN	SN	-3.66	-0.29
131	IFG_L_6_5	CG_R_7_3	SN	SN	-3.87	-0.3
132	IFG_R_6_5	CG_R_7_3	SN	SN	-3.62	-0.28
133	IFG_L_6_6	CG_R_7_3	SN	SN	-4.54	-0.36
134	OrG_R_6_6	CG_R_7_3	DMN	SN	-4.33	-0.34
135	INS_L_6_3	CG_R_7_3	SN	SN	-4.09	-0.32

136	INS_R_6_3	CG_R_7_3	SN	SN	-3.64	-0.29
137	INS_R_6_6	CG_R_7_3	SN	SN	-3.58	-0.28
138	CG_L_7_3	CG_R_7_3	DMN	SN	-3.67	-0.29
139	MVOcC _R_5_2	CG_R_7_3	VIS	SN	-4.19	-0.33
140	IFG_L_6_3	CG_L_7_5	DMN	SN	-3.56	-0.28
141	IFG_L_6_6	CG_L_7_5	SN	SN	-3.73	-0.29
142	PrG_L_6_2	CG_L_7_5	DAN	SN	-3.53	-0.28
143	CG_R_7_5	CG_L_7_5	SN	SN	-3.87	-0.3
144	IFG_L_6_3	CG_L_7_6	DMN	SN	-3.86	-0.3
145	IFG_R_6_4	CG_L_7_6	FPN	SN	-3.54	-0.28
146	LOcC_R_4_2	MVOcC _L_5_1	VIS	VIS	-3.92	-0.31
147	IFG_L_6_3	MVOcC _L_5_2	DMN	VIS	-3.81	-0.3
148	BG_L_6_5	MVOcC _L_5_2	SUB	VIS	-3.68	-0.29
149	SFG_L_7_1	MVOcC _R_5_2	FPN	VIS	-4.21	-0.33
150	SFG_L_7_6	MVOcC _R_5_2	DMN	VIS	-3.9	-0.31
151	MFG_L_7_1	MVOcC _R_5_2	SN	VIS	-3.84	-0.3
152	IFG_L_6_3	MVOcC _R_5_2	DMN	VIS	-4.79	-0.38
153	IFG_L_6_4	MVOcC _R_5_2	DMN	VIS	-3.55	-0.28
154	IFG_R_6_4	MVOcC _R_5_2	FPN	VIS	-4	-0.31
155	IFG_L_6_5	MVOcC _R_5_2	SN	VIS	-3.61	-0.28
156	IFG_L_6_6	MVOcC _R_5_2	SN	VIS	-4.08	-0.32
157	OrG_L_6_6	MVOcC _R_5_2	DMN	VIS	-3.86	-0.3
158	OrG_R_6_6	MVOcC _R_5_2	DMN	VIS	-3.56	-0.28
159	STG_L_6_4	MVOcC _R_5_2	SMN	VIS	-4.17	-0.33
160	STG_R_6_6	MVOcC _R_5_2	DMN	VIS	-3.6	-0.28
161	pSTS_L_2_1	MVOcC _R_5_2	DMN	VIS	-4.43	-0.35
162	pSTS_R_2_1	MVOcC _R_5_2	DMN	VIS	-4.09	-0.32
163	pSTS_L_2_2	MVOcC _R_5_2	SN	VIS	-4	-0.31
164	CG_L_7_6	MVOcC _R_5_2	SN	VIS	-3.53	-0.28
165	BG_L_6_5	MVOcC _R_5_2	SUB	VIS	-4.18	-0.33
166	LOcC_L_4_3	MVOcC _L_5_3	VIS	VIS	-3.85	-0.3
167	PoG_L_4_3	MVOcC _R_5_3	DAN	VIS	-3.86	-0.3
168	PrG_L_6_2	MVOcC _R_5_4	DAN	VIS	-4	-0.31
169	PrG_L_6_3	MVOcC _R_5_4	SMN	VIS	-4.25	-0.33
170	SPL_L_5_5	MVOcC _R_5_4	DAN	VIS	-3.83	-0.3
171	PoG_L_4_3	MVOcC _R_5_4	DAN	VIS	-3.93	-0.31
172	MVOcC _L_5_2	MVOcC _R_5_4	VIS	VIS	-3.57	-0.28
173	SFG_L_7_1	MVOcC _L_5_5	FPN	VIS	-3.93	-0.31
174	SFG_L_7_6	MVOcC _L_5_5	DMN	VIS	-3.63	-0.28
175	MFG_L_7_1	MVOcC _L_5_5	SN	VIS	-3.61	-0.28
176	IFG_L_6_3	MVOcC _L_5_5	DMN	VIS	-4.34	-0.34
177	IFG_L_6_6	MVOcC _L_5_5	SN	VIS	-3.67	-0.29
178	STG_L_6_4	MVOcC _L_5_5	SMN	VIS	-3.85	-0.3
179	pSTS_L_2_1	MVOcC _L_5_5	DMN	VIS	-3.7	-0.29
180	pSTS_R_2_1	MVOcC _L_5_5	DMN	VIS	-3.97	-0.31
181	pSTS_L_2_2	MVOcC _L_5_5	SN	VIS	-3.54	-0.28
182	BG_L_6_5	MVOcC _L_5_5	SUB	VIS	-3.73	-0.29

183	SFG_L_7_1	MVOcC _R_5_5	FPN	VIS	-3.89	-0.31
184	SFG_L_7_6	MVOcC _R_5_5	DMN	VIS	-3.62	-0.28
185	IFG_L_6_3	MVOcC _R_5_5	DMN	VIS	-4.24	-0.33
186	IFG_L_6_6	MVOcC _R_5_5	SN	VIS	-3.72	-0.29
187	STG_L_6_4	MVOcC _R_5_5	SMN	VIS	-4.24	-0.33
188	pSTS_L_2_1	MVOcC _R_5_5	DMN	VIS	-4.03	-0.32
189	pSTS_R_2_1	MVOcC _R_5_5	DMN	VIS	-4.31	-0.34
190	pSTS_L_2_2	MVOcC _R_5_5	SN	VIS	-3.86	-0.3
191	pSTS_R_2_2	MVOcC _R_5_5	SN	VIS	-3.8	-0.3
192	BG_L_6_5	MVOcC _R_5_5	SUB	VIS	-3.51	-0.28
193	FuG_L_3_2	LOcC_L_4_1	VIS	VIS	-3.64	-0.29
194	IPL_L_6_5	LOcC_L_4_1	DAN	VIS	-3.93	-0.31
195	BG_L_6_4	LOcC_L_4_1	SUB	VIS	-3.96	-0.31
196	FuG_L_3_2	LOcC_R_4_1	VIS	VIS	-3.76	-0.29
197	IPL_R_6_1	LOcC_R_4_1	VIS	VIS	-3.85	-0.3
198	IPL_L_6_5	LOcC_R_4_1	DAN	VIS	-4.05	-0.32
199	PrG_R_6_4	LOcC_L_4_2	SMN	DAN	-4.14	-0.32
200	MVOcC _L_5_1	LOcC_L_4_2	VIS	DAN	-3.77	-0.3
201	Hipp_L_2_2	LOcC_L_4_2	SUB	DAN	-3.78	-0.3
202	PrG_L_6_4	LOcC_R_4_2	SMN	VIS	-3.68	-0.29
203	MVOcC _L_5_1	LOcC_R_4_2	VIS	VIS	-3.72	-0.29
204	PoG_L_4_3	LOcC_L_4_3	DAN	VIS	-3.61	-0.28
205	MVOcC _L_5_3	LOcC_R_4_3	VIS	VIS	-4.13	-0.32
206	IFG_L_6_3	LOcC _L_2_1	DMN	VIS	-3.93	-0.31
207	SPL_L_5_4	BG_L_6_2	SMN	SUB	-3.62	-0.28
208	PCun_L_4_3	BG_L_6_2	VIS	SUB	-4.1	-0.32
209	PCun_R_4_3	BG_L_6_2	VIS	SUB	-3.52	-0.28
210	SPL_L_5_4	BG_R_6_2	SMN	SUB	-3.5	-0.27
211	SPL_L_5_4	BG_L_6_4	SMN	SUB	-3.56	-0.28
212	MVOcC _R_5_2	BG_L_6_4	VIS	SUB	-3.53	-0.28
213	SPL_R_5_2	BG_L_6_5	DAN	SUB	-4.09	-0.32
214	PCun_R_4_3	BG_L_6_5	VIS	SUB	-3.86	-0.3
215	CG_L_7_6	BG_L_6_5	SN	SUB	-3.51	-0.28
216	CG_R_7_6	BG_L_6_5	SN	SUB	-3.55	-0.28
217	MVOcC _R_5_2	BG_L_6_5	VIS	SUB	-3.51	-0.28
218	PCun_R_4_3	BG_R_6_5	VIS	SUB	-3.58	-0.28
219	MVOcC _L_5_2	BG_R_6_5	VIS	SUB	-3.61	-0.28
220	MVOcC _R_5_2	BG_R_6_5	VIS	SUB	-4.28	-0.34
221	SPL_L_5_4	BG_L_6_6	SMN	SUB	-3.72	-0.29
222	PCun_L_4_3	BG_L_6_6	VIS	SUB	-3.56	-0.28
223	MVOcC _R_5_3	Tha_L_8_7	VIS	SUB	-3.55	-0.28

Abbreviations: DAN, Dorsal Attention Network; DMN, Default-Mode Network; FPN, Frontoparietal Network; SN, Salience Network; SMN, Sensory-Motor Network; SUB, Subcortex; VIS, Visual Network.

S8. Developmental Stress and Task-Dependent Functional Connectivity

Table S4. Negative associations between prenatal stress and functional connectivity during emotion regulation (NBS-corrected).

Connection	Seed Name	Target Name	Seed Network	Target Network	t	Hedge's g
1	Hipp_R_2_2	SFG_R_7_2	SUB	FPN	-3.61	-0.29
2	IFG_R_6_3	SFG_R_7_4	DMN	DAN	-3.84	-0.3
3	IFG_R_6_2	SFG_R_7_5	FPN	SMN	-3.69	-0.29
4	FuG_R_3_3	SFG_R_7_5	VIS	SMN	-3.53	-0.28
5	Hipp_R_2_2	SFG_R_7_5	SUB	SMN	-3.57	-0.28
6	IFG_R_6_3	SFG_R_7_6	DMN	FPN	-3.61	-0.29
7	ITG_R_7_5	MFG_L_7_1	DAN	SN	-3.59	-0.28
8	ITG_R_7_5	MFG_R_7_4	DAN	FPN	-3.53	-0.28
9	BG_L_6_1	MFG_R_7_4	SUB	FPN	-3.52	-0.28
10	SFG_R_7_4	IFG_L_6_2	DAN	FPN	-3.81	-0.3
11	MVOcC _L_5_5	IFG_L_6_2	VIS	FPN	-3.52	-0.28
12	SFG_R_7_4	IFG_R_6_3	DAN	DMN	-3.53	-0.28
13	PrG_R_6_2	IFG_R_6_3	DAN	DMN	-3.51	-0.28
14	SFG_R_7_4	IFG_L_6_5	DAN	SN	-3.84	-0.3
15	Tha_L_8_1	IFG_R_6_5	SUB	SN	-3.78	-0.3
16	INS_R_6_4	IFG_R_6_6	SN	SN	-3.88	-0.31
17	BG_L_6_1	IFG_R_6_6	SUB	SN	-3.54	-0.28
18	MFG_L_7_6	OrG_R_6_2	DAN	DMN	-3.51	-0.28
19	IFG_R_6_3	PrG_L_6_4	DMN	SMN	-3.87	-0.31
20	Amyg_R_2_2	PrG_L_6_4	SUB	SMN	-3.81	-0.3
21	MVOcC _L_5_4	PrG_R_6_4	VIS	SMN	-3.73	-0.3
22	Amyg_R_2_2	PrG_R_6_4	SUB	SMN	-3.96	-0.31
23	FuG_R_3_3	PrG_R_6_5	VIS	SN	-3.74	-0.3
24	INS_L_6_4	PrG_R_6_5	SN	SN	-3.54	-0.28
25	INS_R_6_4	PrG_R_6_5	SN	SN	-3.62	-0.29
26	MFG_R_7_3	STG_R_6_2	FPN	SMN	-3.61	-0.29
27	INS_R_6_4	STG_R_6_2	SN	SMN	-3.73	-0.3
28	PrG_R_6_3	STG_L_6_3	SMN	SMN	-3.59	-0.28
29	INS_R_6_4	STG_R_6_3	SN	SMN	-3.74	-0.3
30	Tha_L_8_1	STG_R_6_3	SUB	SMN	-3.67	-0.29
31	Tha_L_8_1	STG_L_6_6	SUB	DMN	-3.8	-0.3
32	Tha_L_8_1	STG_R_6_6	SUB	DMN	-4.45	-0.35
33	Tha_L_8_1	MTG_L_4_3	SUB	DAN	-3.52	-0.28
34	Tha_R_8_5	ITG_L_7_3	SUB	LN	-3.55	-0.28
35	BG_L_6_1	ITG_R_7_5	SUB	DAN	-3.88	-0.31
36	BG_R_6_1	ITG_R_7_5	SUB	DAN	-3.94	-0.31
37	BG_L_6_3	ITG_R_7_5	SUB	DAN	-4.06	-0.32
38	BG_R_6_3	ITG_R_7_5	SUB	DAN	-4.29	-0.34
39	BG_R_6_5	ITG_R_7_5	SUB	DAN	-4.05	-0.32
40	MFG_L_7_4	FuG_L_3_2	FPN	VIS	-4.24	-0.34
41	SFG_R_7_4	FuG_R_3_3	DAN	VIS	-3.59	-0.28

42	Tha_R_8_3	FuG_R_3_3	SUB	VIS	-3.53	-0.28
43	Tha_L_8_1	pSTS_R_2_1	SUB	DMN	-3.86	-0.3
44	BG_R_6_1	SPL_L_5_3	SUB	DAN	-3.55	-0.28
45	BG_R_6_3	SPL_R_5_4	SUB	SMN	-3.54	-0.28
46	Tha_L_8_1	IPL_R_6_5	SUB	DMN	-3.55	-0.28
47	IFG_R_6_3	PoG_L_4_1	DMN	SMN	-3.56	-0.28
48	STG_L_6_3	PoG_R_4_4	SMN	SMN	-3.59	-0.28
49	INS_L_6_1	PoG_R_4_4	SMN	SMN	-3.55	-0.28
50	INS_R_6_4	PoG_R_4_4	SN	SMN	-4.18	-0.33
51	Amyg_R_2_2	PoG_R_4_4	SUB	SMN	-3.74	-0.3
52	Tha_L_8_1	PoG_R_4_4	SUB	SMN	-3.63	-0.29
53	Tha_L_8_7	PoG_R_4_4	SUB	SMN	-4.13	-0.33
54	IFG_R_6_2	INS_L_6_1	FPN	SMN	-3.56	-0.28
55	IFG_R_6_3	INS_L_6_1	DMN	SMN	-3.7	-0.29
56	PrG_R_6_3	INS_L_6_1	SMN	SMN	-4.21	-0.33
57	STG_R_6_1	INS_L_6_1	LN	SMN	-3.53	-0.28
58	FuG_R_3_3	INS_L_6_1	VIS	SMN	-3.78	-0.3
59	MFG_L_7_3	INS_L_6_2	FPN	SUB	-3.79	-0.3
60	MFG_L_7_4	INS_L_6_2	FPN	SUB	-3.81	-0.3
61	Tha_L_8_1	INS_L_6_2	SUB	SUB	-3.71	-0.29
62	SFG_R_7_4	INS_L_6_3	DAN	SN	-3.91	-0.31
63	Tha_L_8_1	INS_L_6_3	SUB	SN	-3.56	-0.28
64	PrG_R_6_3	INS_L_6_5	SMN	SMN	-3.54	-0.28
65	Tha_L_8_1	INS_L_6_5	SUB	SMN	-3.81	-0.3
66	FuG_R_3_3	INS_R_6_6	VIS	SN	-3.67	-0.29
67	SFG_L_7_1	CG_L_7_2	FPN	SUB	-3.65	-0.29
68	SFG_L_7_2	CG_L_7_2	DMN	SUB	-3.82	-0.3
69	SFG_R_7_2	CG_L_7_2	FPN	SUB	-3.71	-0.29
70	SFG_L_7_3	CG_L_7_2	DMN	SUB	-4.04	-0.32
71	SFG_R_7_3	CG_L_7_2	DMN	SUB	-3.76	-0.3
72	SFG_L_7_7	CG_L_7_2	DMN	SUB	-4.1	-0.32
73	MFG_L_7_3	CG_L_7_2	FPN	SUB	-4.44	-0.35
74	MFG_R_7_3	CG_L_7_2	FPN	SUB	-4.72	-0.37
75	MFG_L_7_4	CG_L_7_2	FPN	SUB	-4.36	-0.34
76	MFG_R_7_4	CG_L_7_2	FPN	SUB	-3.96	-0.31
77	MFG_L_7_5	CG_L_7_2	DMN	SUB	-4.1	-0.32
78	MFG_L_7_6	CG_L_7_2	DAN	SUB	-3.8	-0.3
79	OrG_R_6_2	CG_L_7_2	DMN	SUB	-4.35	-0.34
80	OrG_L_6_6	CG_L_7_2	DMN	SUB	-3.76	-0.3
81	OrG_R_6_6	CG_L_7_2	DMN	SUB	-3.74	-0.3
82	IPL_L_6_2	CG_L_7_2	FPN	SUB	-4.16	-0.33
83	IPL_R_6_2	CG_L_7_2	FPN	SUB	-3.56	-0.28
84	IPL_L_6_4	CG_L_7_2	DMN	SUB	-4.53	-0.36
85	IPL_R_6_4	CG_L_7_2	FPN	SUB	-3.57	-0.28
86	PCun_L_4_3	CG_L_7_2	VIS	SUB	-4.09	-0.32
87	CG_L_7_7	CG_L_7_2	DMN	SUB	-4.62	-0.36
88	CG_R_7_7	CG_L_7_2	DMN	SUB	-4.51	-0.36

89	MVOcC _L_5_5	CG_L_7_2	VIS	SUB	-4.18	-0.33
90	IFG_R_6_3	CG_L_7_3	DMN	DMN	-3.82	-0.3
91	IPL_L_6_4	CG_L_7_3	DMN	DMN	-3.53	-0.28
92	IFG_R_6_3	CG_R_7_3	DMN	SN	-3.51	-0.28
93	Tha_L_8_1	CG_L_7_5	SUB	SN	-3.52	-0.28
94	Tha_R_8_6	CG_L_7_5	SUB	SN	-3.74	-0.3
95	SFG_R_7_3	LOcC_L_4_4	DMN	VIS	-3.51	-0.28
96	Tha_L_8_7	Amyg_L_2_2	SUB	SUB	-3.58	-0.28
97	MFG_R_7_2	BG_L_6_1	FPN	SUB	-3.66	-0.29
98	MFG_R_7_5	BG_L_6_1	FPN	SUB	-3.75	-0.3
99	IFG_R_6_2	BG_L_6_1	FPN	SUB	-3.71	-0.29
100	IFG_R_6_3	BG_L_6_1	DMN	SUB	-4.18	-0.33
101	pSTS_R_2_2	BG_L_6_1	SN	SUB	-3.67	-0.29
102	PCun_R_4_2	BG_L_6_1	DAN	SUB	-3.87	-0.31
103	Tha_R_8_6	BG_L_6_1	SUB	SUB	-3.81	-0.3
104	MFG_R_7_2	BG_R_6_1	FPN	SUB	-3.83	-0.3
105	IFG_R_6_2	BG_R_6_1	FPN	SUB	-4.07	-0.32
106	IFG_R_6_3	BG_R_6_1	DMN	SUB	-3.84	-0.3
107	PCL_R_2_1	BG_R_6_1	SMN	SUB	-3.77	-0.3
108	SPL_R_5_3	BG_R_6_1	DAN	SUB	-3.71	-0.29
109	IPL_R_6_6	BG_R_6_1	SMN	SUB	-3.56	-0.28
110	Tha_R_8_6	BG_R_6_1	SUB	SUB	-3.51	-0.28
111	IFG_R_6_1	BG_L_6_2	DAN	SUB	-3.69	-0.29
112	IFG_R_6_2	BG_L_6_2	FPN	SUB	-4.06	-0.32
113	IFG_R_6_3	BG_L_6_2	DMN	SUB	-3.84	-0.3
114	ITG_R_7_5	BG_L_6_2	DAN	SUB	-3.65	-0.29
115	IPL_L_6_3	BG_L_6_2	DAN	SUB	-3.52	-0.28
116	Tha_R_8_6	BG_L_6_2	SUB	SUB	-4.33	-0.34
117	IFG_L_6_2	BG_R_6_2	FPN	SUB	-3.6	-0.28
118	IFG_R_6_2	BG_R_6_2	FPN	SUB	-3.69	-0.29
119	IFG_R_6_3	BG_R_6_2	DMN	SUB	-3.7	-0.29
120	ITG_R_7_5	BG_R_6_2	DAN	SUB	-3.69	-0.29
121	Tha_L_8_1	BG_R_6_2	SUB	SUB	-4.25	-0.34
122	STG_R_6_4	BG_L_6_3	SMN	SUB	-3.6	-0.28
123	Tha_R_8_6	BG_L_6_3	SUB	SUB	-3.91	-0.31
124	Tha_R_8_6	BG_R_6_3	SUB	SUB	-3.54	-0.28
125	IFG_R_6_2	BG_L_6_4	FPN	SUB	-3.84	-0.3
126	IFG_R_6_3	BG_L_6_4	DMN	SUB	-3.78	-0.3
127	STG_R_6_4	BG_L_6_4	SMN	SUB	-3.54	-0.28
128	IPL_L_6_3	BG_L_6_4	DAN	SUB	-3.6	-0.28
129	Tha_R_8_6	BG_L_6_4	SUB	SUB	-4.93	-0.39
130	IFG_R_6_2	BG_R_6_4	FPN	SUB	-4.13	-0.33
131	IFG_R_6_3	BG_R_6_4	DMN	SUB	-3.7	-0.29
132	ITG_R_7_5	BG_R_6_4	DAN	SUB	-3.67	-0.29
133	Tha_L_8_1	BG_R_6_4	SUB	SUB	-4.16	-0.33
134	Tha_R_8_6	BG_R_6_4	SUB	SUB	-4.07	-0.32
135	Tha_R_8_8	BG_R_6_4	SUB	SUB	-3.62	-0.29

136	MFG_L_7_3	BG_L_6_5	FPN	SUB	-3.98	-0.31
137	MFG_L_7_4	BG_L_6_5	FPN	SUB	-3.77	-0.3
138	IFG_L_6_3	BG_L_6_5	DMN	SUB	-3.71	-0.29
139	IFG_R_6_3	BG_L_6_5	DMN	SUB	-3.5	-0.28
140	PCL_R_2_1	BG_L_6_5	SMN	SUB	-3.52	-0.28
141	SFG_L_7_1	BG_R_6_5	FPN	SUB	-3.86	-0.31
142	MFG_R_7_2	BG_R_6_5	FPN	SUB	-4.04	-0.32
143	MFG_L_7_3	BG_R_6_5	FPN	SUB	-4.08	-0.32
144	MFG_L_7_4	BG_R_6_5	FPN	SUB	-4.12	-0.33
145	MFG_R_7_5	BG_R_6_5	FPN	SUB	-3.76	-0.3
146	IFG_R_6_3	BG_R_6_5	DMN	SUB	-3.74	-0.3
147	PCL_R_2_1	BG_R_6_5	SMN	SUB	-3.67	-0.29
148	SPL_R_5_3	BG_R_6_5	DAN	SUB	-3.75	-0.3
149	CG_R_7_6	BG_R_6_5	SN	SUB	-3.7	-0.29
150	IFG_R_6_1	BG_L_6_6	DAN	SUB	-3.84	-0.3
151	IFG_L_6_2	BG_L_6_6	FPN	SUB	-3.8	-0.3
152	IFG_R_6_2	BG_L_6_6	FPN	SUB	-4.28	-0.34
153	IFG_R_6_3	BG_L_6_6	DMN	SUB	-4.44	-0.35
154	IFG_R_6_6	BG_L_6_6	SN	SUB	-3.71	-0.29
155	ITG_R_7_5	BG_L_6_6	DAN	SUB	-3.71	-0.29
156	IPL_L_6_3	BG_L_6_6	DAN	SUB	-3.91	-0.31
157	Tha_L_8_1	BG_L_6_6	SUB	SUB	-5	-0.4
158	Tha_R_8_1	BG_L_6_6	SUB	SUB	-3.71	-0.29
159	Tha_R_8_4	BG_L_6_6	SUB	SUB	-3.88	-0.31
160	Tha_L_8_6	BG_L_6_6	SUB	SUB	-3.65	-0.29
161	Tha_R_8_6	BG_L_6_6	SUB	SUB	-5.13	-0.41
162	Tha_L_8_7	BG_L_6_6	SUB	SUB	-3.85	-0.3
163	Tha_R_8_8	BG_L_6_6	SUB	SUB	-3.94	-0.31
164	IFG_R_6_2	BG_R_6_6	FPN	SUB	-3.64	-0.29
165	IFG_R_6_3	BG_R_6_6	DMN	SUB	-4.19	-0.33
166	IFG_R_6_6	BG_R_6_6	SN	SUB	-4.07	-0.32
167	PrG_R_6_3	BG_R_6_6	SMN	SUB	-3.72	-0.29
168	Tha_L_8_1	BG_R_6_6	SUB	SUB	-4.89	-0.39
169	Tha_R_8_4	BG_R_6_6	SUB	SUB	-3.67	-0.29
170	Tha_L_8_5	BG_R_6_6	SUB	SUB	-3.72	-0.29
171	Tha_L_8_6	BG_R_6_6	SUB	SUB	-3.75	-0.3
172	Tha_R_8_6	BG_R_6_6	SUB	SUB	-3.95	-0.31
173	Tha_L_8_7	BG_R_6_6	SUB	SUB	-3.98	-0.31
174	Tha_R_8_8	BG_R_6_6	SUB	SUB	-4.16	-0.33
175	SFG_R_7_4	Tha_L_8_1	DAN	SUB	-4.07	-0.32
176	IFG_L_6_2	Tha_L_8_1	FPN	SUB	-3.89	-0.31
177	SFG_L_7_1	Tha_R_8_1	FPN	SUB	-3.65	-0.29
178	SFG_R_7_4	Tha_R_8_1	DAN	SUB	-4.35	-0.34
179	SFG_L_7_5	Tha_R_8_1	SMN	SUB	-3.65	-0.29
180	SFG_L_7_6	Tha_R_8_1	DMN	SUB	-3.71	-0.29
181	MFG_L_7_3	Tha_R_8_1	FPN	SUB	-3.7	-0.29
182	MFG_R_7_3	Tha_R_8_1	FPN	SUB	-3.62	-0.29

183	MFG_L_7_4	Tha_R_8_1	FPN	SUB	-3.94	-0.31
184	MFG_R_7_5	Tha_R_8_1	FPN	SUB	-3.73	-0.29
185	IFG_R_6_3	Tha_R_8_1	DMN	SUB	-3.64	-0.29
186	OrG_R_6_6	Tha_R_8_1	DMN	SUB	-4.71	-0.37
187	PrG_L_6_2	Tha_R_8_1	DAN	SUB	-3.54	-0.28
188	PrG_R_6_3	Tha_R_8_1	SMN	SUB	-3.86	-0.3
189	PCL_R_2_1	Tha_R_8_1	SMN	SUB	-3.61	-0.29
190	ITG_L_7_3	Tha_R_8_1	LN	SUB	-3.58	-0.28
191	SPL_R_5_3	Tha_R_8_1	DAN	SUB	-3.63	-0.29
192	IPL_L_6_3	Tha_R_8_1	DAN	SUB	-3.8	-0.3
193	IPL_R_6_3	Tha_R_8_1	DAN	SUB	-3.67	-0.29
194	IPL_L_6_4	Tha_R_8_1	DMN	SUB	-4.08	-0.32
195	IPL_R_6_4	Tha_R_8_1	FPN	SUB	-4.3	-0.34
196	SFG_R_7_4	Tha_L_8_2	DAN	SUB	-3.52	-0.28
197	IFG_R_6_3	Tha_L_8_2	DMN	SUB	-3.56	-0.28
198	ITG_R_7_5	Tha_L_8_2	DAN	SUB	-3.75	-0.3
199	Tha_L_8_1	Tha_L_8_2	SUB	SUB	-4.59	-0.36
200	Tha_R_8_6	Tha_L_8_2	SUB	SUB	-4.95	-0.39
201	Tha_L_8_7	Tha_L_8_2	SUB	SUB	-4.05	-0.32
202	Tha_R_8_8	Tha_L_8_2	SUB	SUB	-4.33	-0.34
203	IFG_L_6_2	Tha_R_8_2	FPN	SUB	-3.92	-0.31
204	IFG_L_6_3	Tha_R_8_2	DMN	SUB	-4.2	-0.33
205	IFG_R_6_3	Tha_L_8_3	DMN	SUB	-3.54	-0.28
206	Tha_L_8_1	Tha_L_8_3	SUB	SUB	-3.72	-0.29
207	Tha_R_8_6	Tha_L_8_3	SUB	SUB	-4.34	-0.34
208	SFG_R_7_4	Tha_R_8_3	DAN	SUB	-3.83	-0.3
209	OrG_R_6_6	Tha_R_8_3	DMN	SUB	-3.85	-0.3
210	IFG_L_6_3	Tha_R_8_4	DMN	SUB	-3.72	-0.29
211	MFG_R_7_3	Tha_L_8_5	FPN	SUB	-3.56	-0.28
212	OrG_R_6_6	Tha_L_8_5	DMN	SUB	-3.58	-0.28
213	OrG_R_6_6	Tha_R_8_5	DMN	SUB	-3.77	-0.3
214	IFG_R_6_4	Tha_L_8_7	FPN	SUB	-3.5	-0.28
215	MFG_L_7_3	Tha_R_8_7	FPN	SUB	-3.91	-0.31
216	MFG_R_7_3	Tha_R_8_7	FPN	SUB	-3.55	-0.28
217	PrG_R_6_3	Tha_R_8_7	SMN	SUB	-3.61	-0.29
218	ITG_L_7_3	Tha_R_8_7	LN	SUB	-3.66	-0.29
219	IPL_R_6_4	Tha_R_8_7	FPN	SUB	-3.6	-0.28
220	SFG_R_7_4	Tha_L_8_8	DAN	SUB	-4.14	-0.33
221	IFG_L_6_2	Tha_L_8_8	FPN	SUB	-4.21	-0.33
222	IFG_R_6_2	Tha_L_8_8	FPN	SUB	-3.55	-0.28
223	IFG_L_6_3	Tha_L_8_8	DMN	SUB	-3.76	-0.3
224	IFG_R_6_3	Tha_L_8_8	DMN	SUB	-3.55	-0.28
225	SFG_R_7_4	Tha_R_8_8	DAN	SUB	-3.53	-0.28
226	SFG_L_7_6	Tha_R_8_8	DMN	SUB	-3.71	-0.29
227	IFG_L_6_2	Tha_R_8_8	FPN	SUB	-4.18	-0.33
228	IFG_L_6_3	Tha_R_8_8	DMN	SUB	-3.85	-0.3
229	IFG_R_6_3	Tha_R_8_8	DMN	SUB	-3.64	-0.29

230	IFG_R_6_4	Tha_R_8_8	FPN	SUB	-3.74	-0.3
231	OrG_R_6_6	Tha_R_8_8	DMN	SUB	-5	-0.39
232	PrG_R_6_3	Tha_R_8_8	SMN	SUB	-3.88	-0.31
233	PCL_R_2_1	Tha_R_8_8	SMN	SUB	-3.52	-0.28
234	SPL_R_5_3	Tha_R_8_8	DAN	SUB	-3.54	-0.28
235	IPL_R_6_4	Tha_R_8_8	FPN	SUB	-3.56	-0.28
236	Tha_R_8_6	Tha_R_8_8	SUB	SUB	-3.91	-0.31

Abbreviations: DAN, Dorsal Attention Network; DMN, Default-Mode Network; FPN, Frontoparietal Network; LH, left hemisphere; LN, Limbic Network; RH, right hemisphere; SN, Salience Network; SMN, Sensory-Motor Network; SUB, Subcortex; VIS, Visual Network.

Table S5. Negative associations between childhood stress and functional connectivity during emotion regulation (NBS-corrected)

Connection	Seed Name	Target Name	Seed Network	Target Network	t	Hedge's g
1	MFG_R_7_6	SFG_R_7_4	DAN	DAN	-3.52	-0.17
2	Tha_R_8_5	SFG_R_7_4	SUB	DAN	-3.51	-0.17
3	PoG_L_4_3	OrG_L_6_2	DAN	DMN	-3.77	-0.18
4	INS_R_6_6	STG_L_6_1	SN	LN	-3.81	-0.18
5	MTG_R_4_4	STG_R_6_1	DMN	LN	-3.58	-0.17
6	PCun_R_4_2	STG_R_6_1	DAN	LN	-3.51	-0.17
7	PoG_L_4_2	STG_R_6_1	SMN	LN	-3.84	-0.18
8	INS_R_6_6	STG_R_6_1	SN	LN	-3.67	-0.18
9	BG_L_6_4	STG_R_6_1	SUB	LN	-3.7	-0.18
10	Tha_R_8_8	MTG_R_4_1	SUB	FPN	-3.66	-0.18
11	Tha_R_8_8	MTG_R_4_2	SUB	DMN	-3.62	-0.17
12	Tha_R_8_8	ITG_L_7_1	SUB	LN	-4.21	-0.2
13	SFG_R_7_4	ITG_L_7_3	DAN	LN	-3.65	-0.17
14	BG_R_6_2	ITG_L_7_3	SUB	LN	-3.86	-0.18
15	Tha_L_8_8	ITG_L_7_3	SUB	LN	-3.62	-0.17
16	Tha_R_8_8	ITG_L_7_3	SUB	LN	-3.73	-0.18
17	MVOcC _R_5_5	ITG_L_7_4	VIS	DMN	-3.59	-0.17
18	Tha_R_8_1	ITG_L_7_4	SUB	DMN	-4.49	-0.21
19	Tha_R_8_5	ITG_L_7_4	SUB	DMN	-3.51	-0.17
20	Tha_L_8_7	ITG_L_7_4	SUB	DMN	-3.7	-0.18
21	Tha_R_8_8	ITG_L_7_4	SUB	DMN	-4.59	-0.22
22	Tha_R_8_8	ITG_R_7_4	SUB	LN	-3.97	-0.19
23	Tha_R_8_8	ITG_L_7_6	SUB	FPN	-3.82	-0.18
24	MFG_L_7_5	ITG_R_7_6	DMN	FPN	-3.51	-0.17
25	PoG_L_4_3	ITG_R_7_6	DAN	FPN	-3.56	-0.17
26	MVOcC _L_5_1	ITG_R_7_6	VIS	FPN	-3.66	-0.18
27	Tha_R_8_8	ITG_R_7_6	SUB	FPN	-4.65	-0.22
28	PoG_L_4_3	ITG_L_7_7	DAN	LN	-3.99	-0.19
29	INS_R_6_3	ITG_L_7_7	SN	LN	-3.74	-0.18
30	Tha_R_8_1	ITG_L_7_7	SUB	LN	-3.54	-0.17
31	Tha_R_8_8	ITG_L_7_7	SUB	LN	-4.8	-0.23
32	Tha_R_8_8	ITG_R_7_7	SUB	LN	-4.69	-0.22
33	PoG_L_4_2	PhG_L_6_5	SMN	LN	-3.51	-0.17
34	INS_R_6_3	INS_L_6_2	SN	SUB	-3.77	-0.18
35	STG_R_6_1	Tha_L_8_1	LN	SUB	-4.11	-0.2
36	STG_R_6_1	Tha_L_8_2	LN	SUB	-3.65	-0.17
37	STG_R_6_1	Tha_L_8_4	LN	SUB	-3.9	-0.19
38	MTG_R_4_1	Tha_L_8_7	FPN	SUB	-3.64	-0.17
39	MFG_R_7_7	Tha_L_8_8	FPN	SUB	-3.91	-0.19
40	STG_R_6_1	Tha_L_8_8	LN	SUB	-3.6	-0.17
41	STG_R_6_1	Tha_R_8_8	LN	SUB	-3.76	-0.18

Abbreviations: DAN, Dorsal Attention Network; DMN, Default-Mode Network; FPN, Frontoparietal Network; LH, left hemisphere; LN, Limbic Network; RH, right hemisphere; SN, Salience Network; SMN, Sensory-Motor Network; SUB, Subcortex; VIS, Visual Network.

Table S6. Negative associations between adolescence stress and functional connectivity during emotion regulation (NBS-corrected).

Connection	Seed Name	Target Name	Seed Network	Target Network	t	Hedge's g
1	LOcC _R_2_1	OrG_L_6_5	VIS	LN	-3.98	-0.20
2	LOcC_R_4_3	LOcC_R_4_1	VIS	VIS	-3.63	-0.18
3	LOcC _L_2_2	LOcC_R_4_1	VIS	VIS	-4.17	-0.21
4	LOcC _R_2_1	LOcC_R_4_3	VIS	VIS	-4.19	-0.21
5	LOcC _L_2_2	LOcC_R_4_3	VIS	VIS	-3.95	-0.20

Abbreviations: LN, Limbic Network; VIS, Visual Network.

S9. Brain-Behavior Relationship

Table S7. Mass univariate analysis (OLS) for connectivity parameters related to childhood stress and externalizing psychopathology relationship.

Time	Seed	Target	β	r^2	FDR-p
T11	Tha_R_8_8	ITG_L_7_3	-4	0.06	0.036
	PoG_L_4_2	PhG_L_6_5	-2.88	0.05	0.036
	STG_R_6_1	Tha_L_8_1	-1.89	0.05	0.036
COVID-I: April 2020	Tha_R_8_8	ITG_L_7_3	-3.97	0.08	0.046
COVID-II: June 2020	INS_R_6_6	STG_R_6_1	-3.92	0.07	0.017
	BG_L_6_4	STG_R_6_1	-4.33	0.06	0.03
	Tha_R_8_8	ITG_L_7_3	-4.26	0.08	0.011
	PoG_L_4_2	PhG_L_6_5	-3.97	0.11	0.007
	STG_R_6_1	Tha_L_8_1	-2.23	0.08	0.011
	STG_R_6_1	Tha_L_8_2	-4.26	0.1	0.008
	STG_R_6_1	Tha_L_8_4	-1.7	0.07	0.017
	STG_R_6_1	Tha_L_8_8	-2.99	0.08	0.011
	STG_R_6_1	Tha_R_8_8	-2.6	0.08	0.011
COVID-III: November 2020	Tha_R_8_8	ITG_L_7_3	-4.77	0.09	0.039

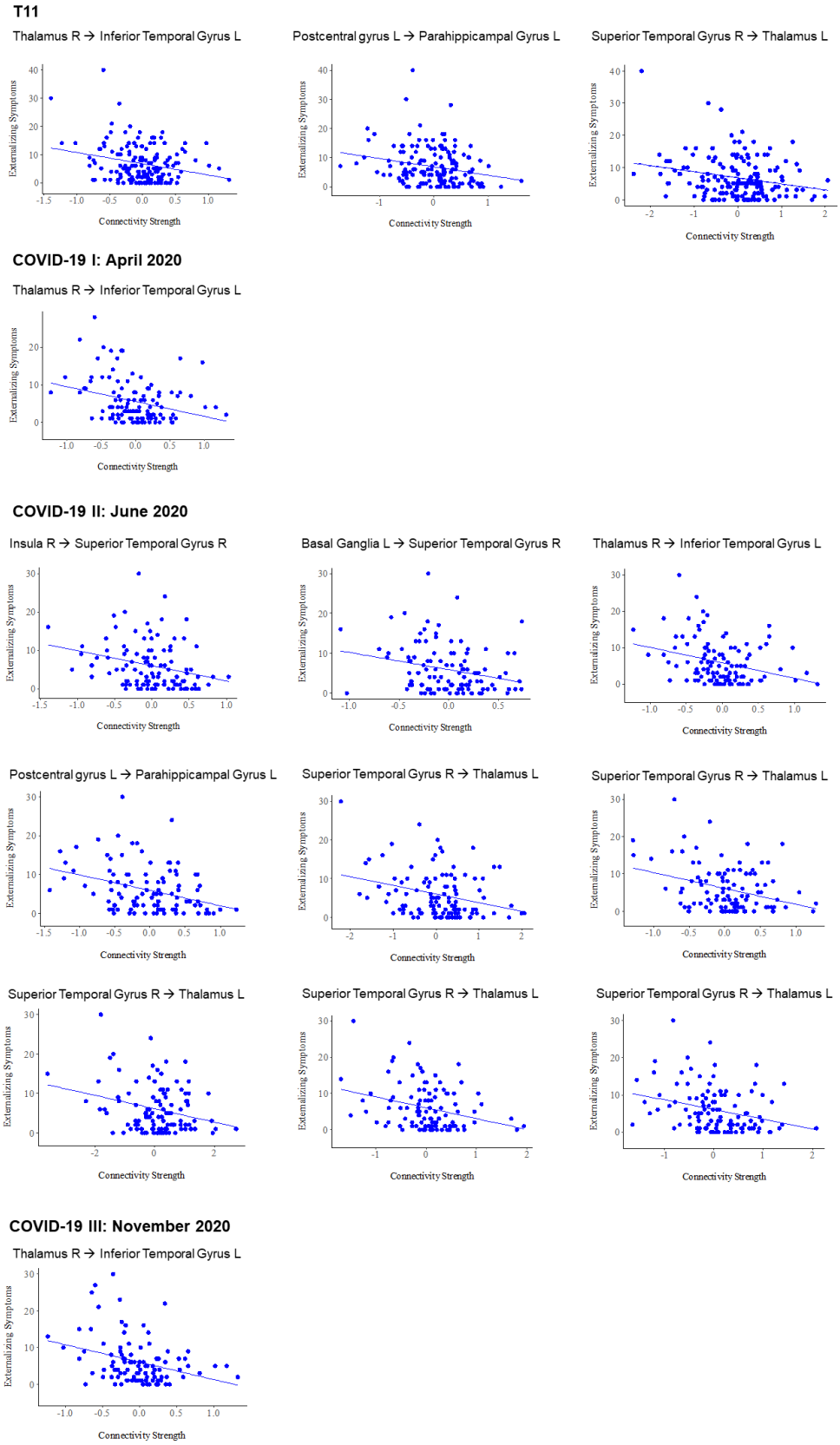

Figure S6. Associations between adulthood externalizing symptoms and connectivity parameters related to higher childhood stress.

S10. Replication Analysis

Whole-brain region-to-region connectivity requires a selection of a parcellation map, which could further introduce heterogeneity due to the subjective selection process (Hallquist & Hillary, 2018). To reduce this bias in our connectivity analyses, we repeated our analyses using two commonly used brain atlases in addition to Brainnetome atlas: Automated Anatomical Labelling (Rolls et al., 2020) representing anatomical parcellation and Schaefer atlas (Schaefer et al., 2018) representing functional parcellation with similar features (e.g., region number, network assignment). Since the Schafer atlas did not include subcortical regions, we combined it with the Melbourne subcortex atlas (Tian et al., 2020).

Table S8. Distribution of regional categories across the parcellation maps.

	AAL (n=164)	Brainnetome (n=246)	Schafer (n=232)
Frontal	24	48	38
Temporal	14	54	31
Occipital	12	26	29
Parietal	10	27	35
Sensory-Motor	14	29	44
Insula	2	12	8
Cingulum	10	14	15
Subcortex	40 (28 Thalamus)	36 (16 Thalamus)	32 (4 Thalamus)
Midbrain	12	0	0
Cerebellum	26	0	0

At uncorrected level ($p < 0.001$), there were striking similarities in terms of adversity-related alterations across the parcellation maps even though they differ from each other in terms of some important features such as total number of regions, parcellated regions and cluster sizes (Table S10). However, these similarities were reduced when we applied multiple testing correction with Network Based Statistic

(NBS). For example, we found 274 connectivity alterations for prenatal stress when we used Schaefer atlas ($p < 0.001$, uncorrected).

The results were comparable with AAL (n=186) and Brainnetome (n=345) atlases (Figure S7), however, these results did not survive the correction while the results from the other two atlases survived. A similar conclusion can be made for the results regarding childhood stress, where only Brainnetome and Schafer survived the correction (Figure S9). Lastly, we found only a few connectivity alterations related to adolescence stress, which survived the correction only with the Brainnetome atlas. Detailed results and comparisons are reported below.

In conclusion, we identified similar stress-related alterations across different parcellation schemes, however, similarities were more pronounced before the correction for multiple comparisons. These results suggest that using different parcellation schemes and reporting shared and distinct patterns could help to alleviate the heterogeneity induced by parcellation map choice and increase the generalizability of the findings. In addition, our findings show that we still need more advanced multiple testing correction methods. Classical approaches such as Bonferroni can be conservative since whole-brain connectivity requires testing thousands of connection parameters. The NBS provides significant power compared to conservative approaches, especially when the contrast-to-noise ratio is low (Zalesky et al., 2010). However, it has its own limitations. First, there is no definitive rule for how to choose a threshold for determining suprathreshold connections. Second, it assumes that connections must form a component and tests the significance of a component rather than single connections constituting the component (Zalesky et al., 2010). An alternative approach can be calculating and reporting effect sizes in addition to p values. In this way, researchers can account for measurement uncertainty, which can

reduce the bias while interpreting their results (Gerchen et al., 2021). Taken together, a selection of a parcellation map inevitably introduces bias, which can be remedied by utilizing a replication atlas and developing advanced methodological approaches for multiple testing correction.

Prenatal Stress

Prenatal and newborn stress was negatively associated with functional connectivity in subcortical and frontal regions (Figure S7). In specific, outgoing connections from frontal regions to subcortex and outgoing connections from subcortex to other regions were affected. Subcortical connections included thalamus and striatum mostly. At network level, these alterations corresponded to outgoing connections from frontoparietal network (FPN), dorsal attention network (DAN), and DMN to subcortex and outgoing connections from subcortex to several networks (Figure S8).

Although comparable connectivity alterations were present in Schaefer Atlas at uncorrected level ($p < 0.001$), none of those connections survived NBS correction (Figure S7A).

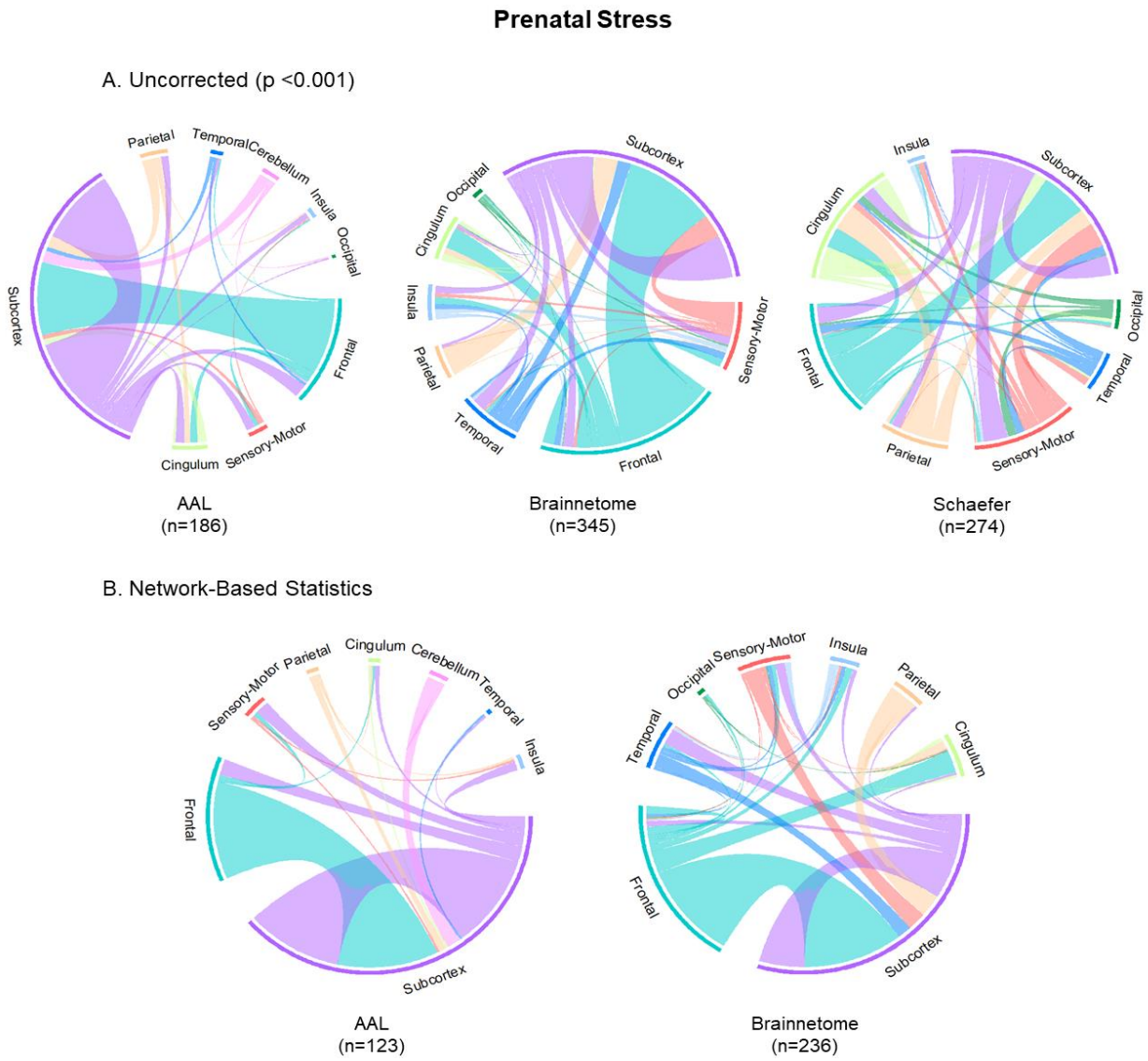

Figure S7. Negative associations between prenatal stress and functional connectivity during emotion regulation at uncorrected level (A) and after network- based statistic correction (B). N represents number of connections. Each region category is assigned to a specific color. Bundle color represents directionality. Connections arising from the source region are depicted with the color of the source region.

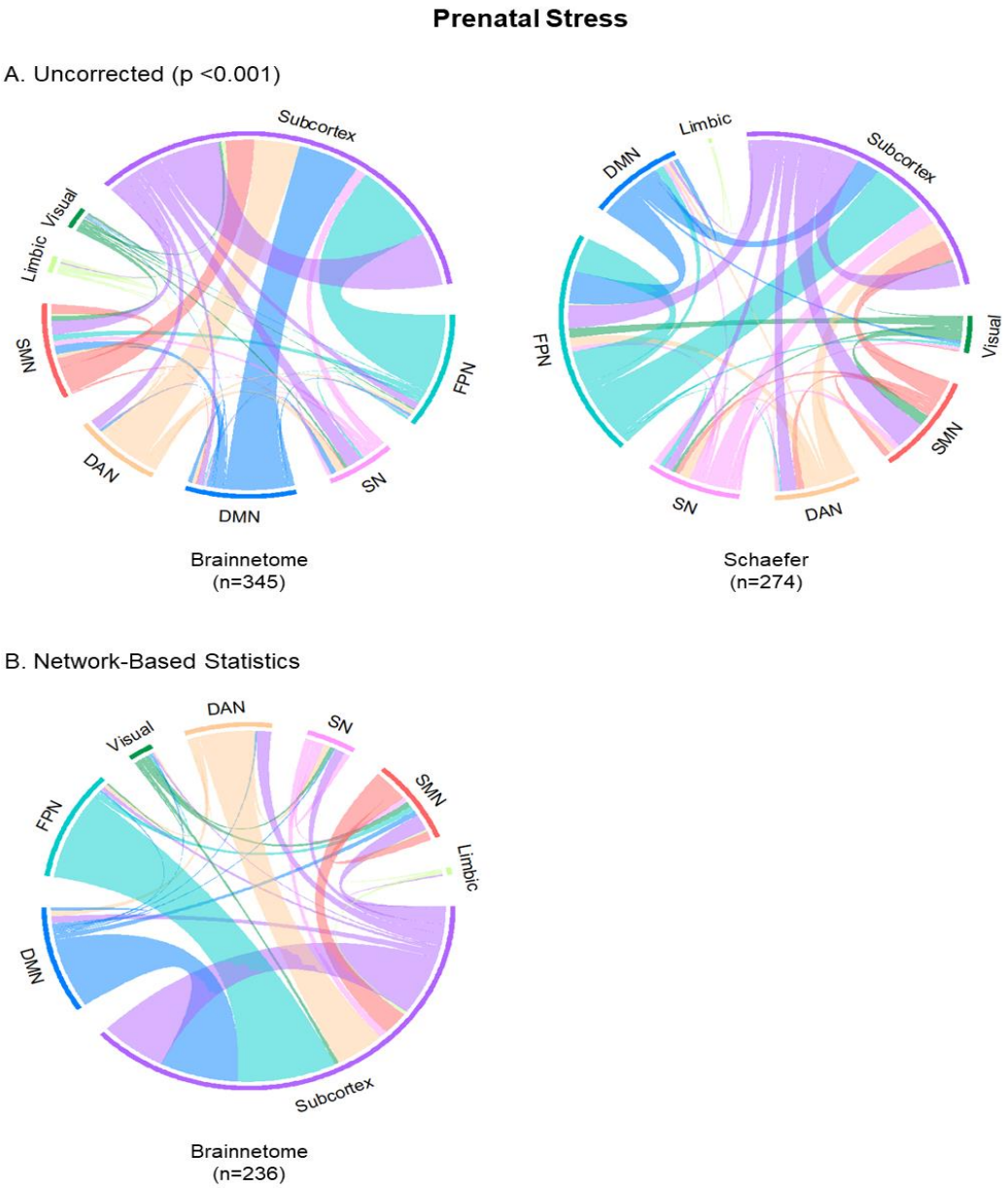

Figure S8. Negative associations between prenatal stress and within and between network connectivity during emotion regulation. N represents number of connections. Each network is assigned to a specific color. Bundle color represents directionality. Connections arising from the source network are depicted with the color of the source network. All results were corrected with network-based statistic. Abbreviations: DAN, dorsal-attention network; DMN, default-mode network; FPN, frontoparietal network; SMN, sensory-motor network; SN, salience network.

Childhood Stress

Childhood stress was negatively associated with functional connectivity in subcortical, temporal and to lesser extent frontal regions (Figure S8). Subcortical regions included mostly thalamus. These alterations corresponded to connections from subcortex to several networks including DMN and attention networks (FPN, DAN) (Figure S9).

Although similar alterations were present in AAL Atlas at uncorrected level ($p < 0.001$), none of those connections survived NBS correction (Figure S8A).

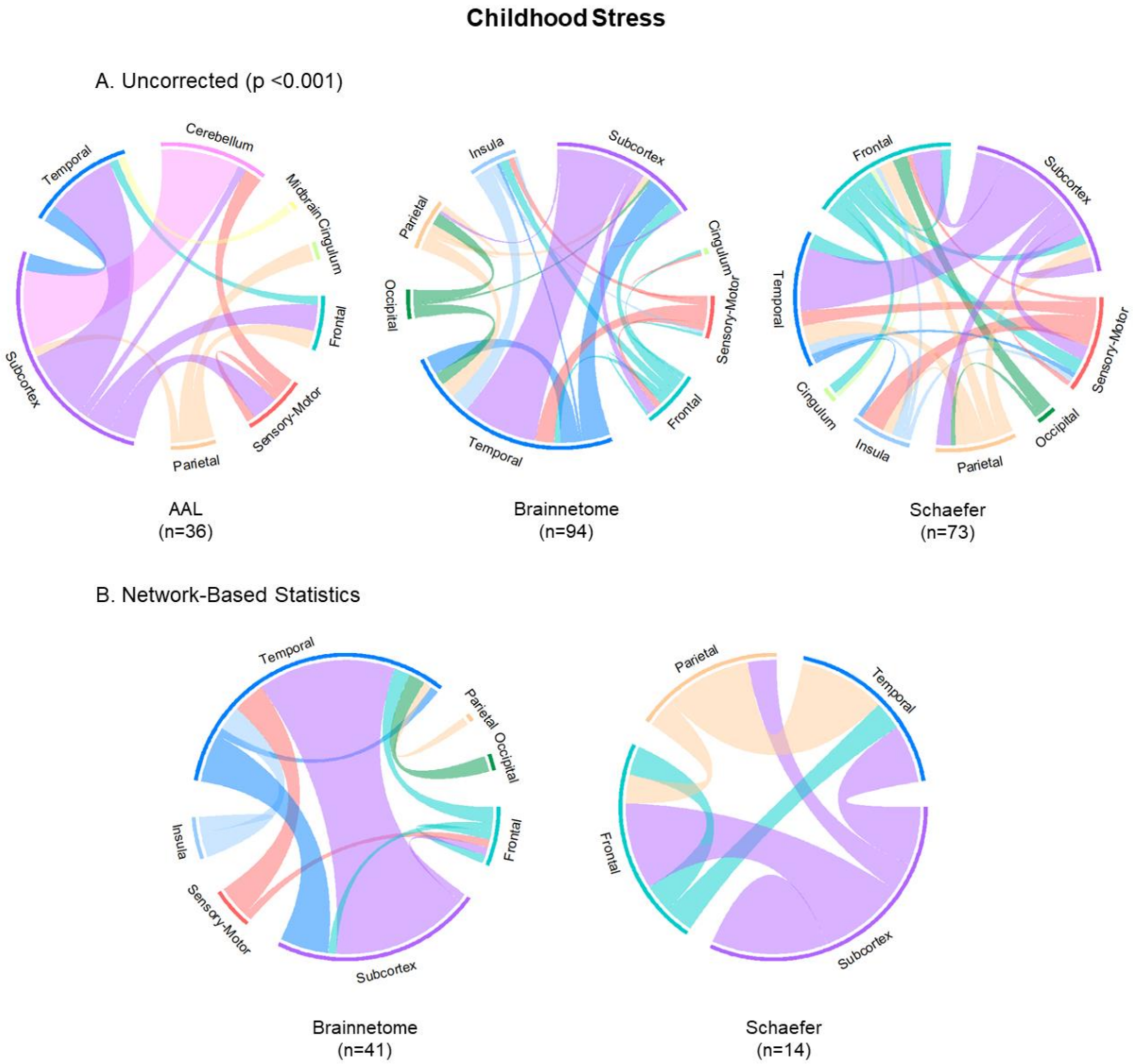

Figure S9. Negative associations between childhood stress and functional connectivity during emotion regulation at uncorrected level (A) and after network-based statistic correction (B). N represents number of connections. Each region category is assigned to a specific color. Bundle color represents directionality. Connections arising from the source region are depicted with the color of the source region.

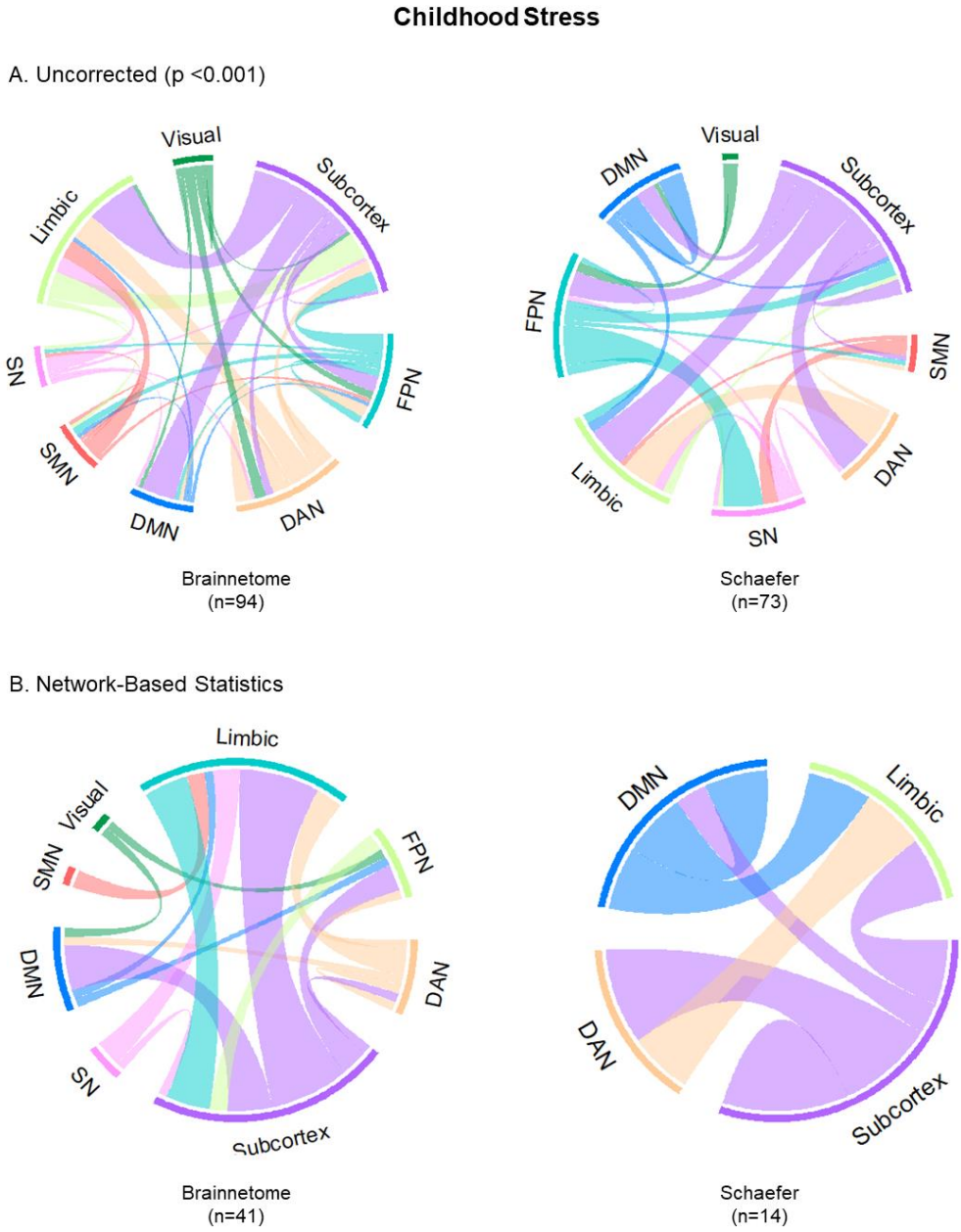

Figure S10. Negative associations between childhood stress and within and between network connectivity during emotion regulation. N represents number of connections. Each network is assigned to a specific color. Bundle color represents directionality. Connections arising from the source network are depicted with the color of the source network. All results were corrected with network-based statistic. Abbreviations: DAN, dorsal-attention network; DMN, default-mode network; FPN, frontoparietal network; SMN, sensory-motor network; SN, salience network.

Adolescence Stress

Only a few connections were related to adolescence stress across the atlases at uncorrected level (p <0.001). We identified five connections for the AAL atlas (3 positive and 2 negative associations), twelve connections for the Brainnetome atlas (5 positive and 7 negative associations) and nine connections for the Schafer atlas (7 positive and 2 negative associations). Only Brainnetome results survived the correction (5 negative associations, Figure S10). However, similar connections were not found in the other atlases at uncorrected level.

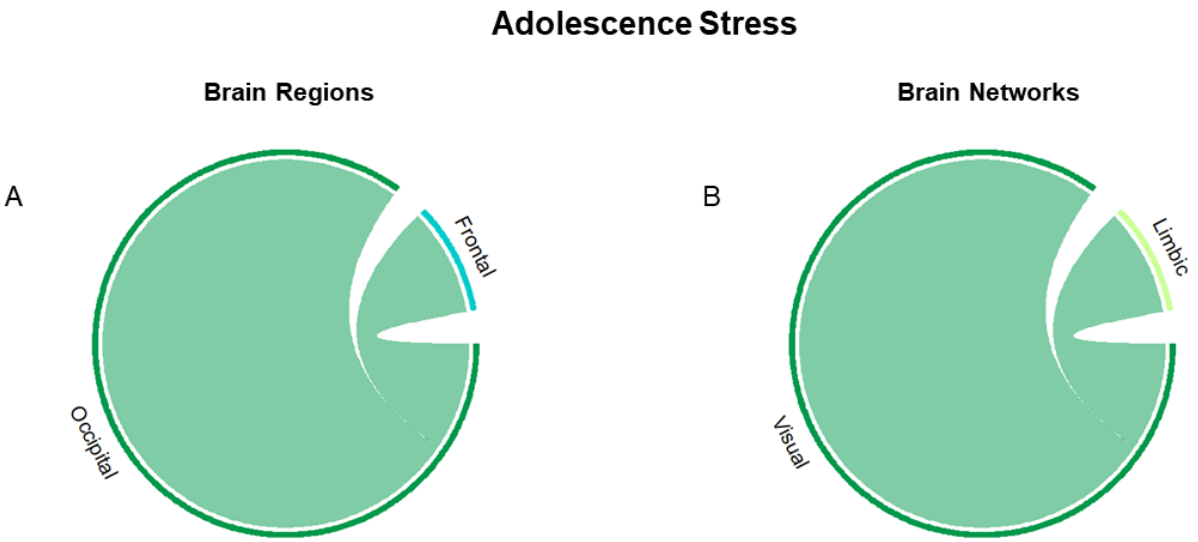

Figure S11. Negative associations between adolescence stress and functional connectivity during emotion regulation (5 connections in total). Each region and network category is assigned to a specific color. Bundle color represents directionality. Connections arising from the source region are depicted with the color of the source region. All results were corrected with network-based statistics.

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