Friendship stress buffering in young people with childhood adversity

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Chapter 1

General Introduction

Climate Change Is Scaring Kids. Here's How to Talk to Them

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Parents of 545 Children Separated at the Border Cannot Be Found

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Over 200,000 Minors Abused by Clergy in France Since 1950, Report Estimates

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After Nonbinary Student's Death, Schools Chief Defends Restrictive Gender Policies

February 23, 2024

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Sugar in India, Fueled by Child Marriage and Hysterectomies

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Finland School Shooting's Motive Was Bullying, Police Say

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Mental Health and Substance Use Disorders Often Go Untreated for Parents on Medicaid

April 19, 2024

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Childhood adversity is ubiquitous. Approximately 60% of all young people growing up worldwide are exposed to at least one form of childhood adversity by age 18 (Madigan et al., 2023). This includes often co-occurring experiences such as abuse or neglect, parental mental illness, severe poverty, bullying, or exposure to war (Brown et al., 2019; Dong et al., 2004). Chronic and repeated exposure to these toxic stressors has cascading life-altering consequences, leading to increased risks for psychopathology, cognitive deficits, chronic diseases, socioeconomic inequalities, transgressive behaviors, and premature mortality (Gilbert et al., 2009; Grummitt et al., 2021; Kessler et al., 2010). Furthermore, the societal costs are staggering, with adverse childhood experiences contributing to economic burdens and strained healthcare systems (K. Hughes et al., 2021; Peterson et al., 2018). That said, childhood adversity is a preventable public health issue, underscoring the importance to identify, understand, and address the factors that put young people at risk for and protect them from its detrimental effects. This dissertation focuses on the protective role of friendships in youth mental health following childhood adversity, contributing to a deeper mechanistic understanding of how these social relationships help buffer the negative effects of stress.

Childhood Adversity

Childhood adversity refers to stressful and potentially traumatic experiences during childhood or adolescence (before age 18) that represent a deviation from what is typically considered a normative environmental context (Cicchetti & Valentino, 2006; McLaughlin, 2016; Nelson & Gabard-Durnam, 2020). This encompasses a range of often co-occurring experiences, from maltreatment, such as exposure to abuse or neglect, to household challenges, which involve exposure to a caregiver experiencing issues such as substance misuse, domestic violence, or divorce, to various other forms of stressful experiences, which can include but is not limited to bullying, discrimination, natural disasters, and refugee or wartime experiences (Brown et al., 2019; K. Hughes et al., 2017; Nelson et al., 2020).

Childhood adversity is the product of several interconnected factors, including social, cultural, economic, environmental, and biological influences, occurring in every society around the world (Madigan et al., 2023; Sethi et al., 2013). Risk factors exist at multiple levels. On an individual level, examples include families with young, single caregivers from lower socioeconomic backgrounds with limited educational opportunities (Crouch et al., 2019; K. Hughes et al., 2017). At the community level, risks are associated with residing in socioeconomically disadvantaged neighborhoods (Kohen et al., 2008), while at the societal level, adverse outcomes may be influenced by cultural norms, such as the approval of physical punishment for disciplining children (Gershoff et al., 2018). Global prevalence estimates from 546,458 adults across 22 countries spanning all continents indicate that approximately six in ten individuals retrospectively self-

reported experiencing at least one form of adversity during childhood or adolescence, with higher rates of particularly severe adversity among those with a history of mental health conditions (47.5%), low-income households (40.5%), and minoritized racial/ethnic groups (26.6%) (Madigan et al., 2023). However, the actual prevalence of childhood adversity is likely higher, as most studies are conducted in the Global North, with many cases unrecorded due to underreporting or societal stigma (Kessler et al., 2009; Meinck et al., 2016; Stoltenborgh et al., 2013).

Two main approaches are currently used to operationalize childhood adversity: cumulative risk and dimensional models of adversity. The prevailing cumulative risk approach focuses on the total number of distinct adverse experiences a young person has encountered, summing these into a cumulative risk score where higher scores signal an increased likelihood of long-term negative health consequences, such as psychopathology (Evans et al., 2013; Felitti et al., 1998). This approach emphasizes stress dysregulation (i.e., altered psychological or physiological responses to stress) as the common, primary mechanism linking childhood adversity with later-life psychopathology (Evans & Kim, 2007; Evans et al., 2013).

More recently, dimensional models of adversity have gained traction as an alternative to the cumulative risk approach. These models aim to expand on the frequently invoked stress pathways by identifying additional mechanisms, particularly learning processes, through which distinct features of adversity shape psychopathology risk (McLaughlin & Sheridan, 2016). This dimensional approach assesses the frequency and severity of childhood adversity and focuses on three core underlying dimensions of experiences that are shared across different types of adversity: threat/harshness (involving harm or threat of harm to oneself and others), deprivation (involving absence of expected cognitive and social stimulation), and, more recently, unpredictability (involving spatial-temporal variation in threat) (Belsky et al., 2012; Berman et al., 2022; McLaughlin et al., 2021; Sheridan & McLaughlin, 2014).

Both approaches have unique strengths and contribute complementary insights (McLaughlin et al., 2021; K. E. Smith & Pollak, 2021). The cumulative risk approach offers a straightforward and widely applicable framework, highlighting the additive effect of adversity on later-life psychopathology. Meanwhile, the dimensional approach offers a more nuanced perspective, elucidating how specific features of adversity differentially affect mechanistic pathways that contribute to increased psychopathology risk. Given that dimensional models are evolving frameworks, further research is needed to refine and update these models based on new insights, particularly as their predictive accuracy regarding later-life functioning remains insufficiently understood (McLaughlin et al., 2021).

Consequences of Childhood Adversity

Childhood adversity is associated with a range of deleterious, far-reaching, and long-lasting health and developmental consequences (S. E. Fox et al., 2010; Shonkoff, 2012). It is considered a major contributor to both morbidity and premature mortality (Grummitt et al., 2021; Rod et al., 2020). A systematic review of 19 meta-analyses with more than 20 million participants estimated that childhood adversity accounted for approximately 15% of the total US mortality rate in 2019, translating to around 439,072 deaths (Grummitt et al., 2021). This high mortality rate was associated with several leading causes of death, including suicide attempts, cardiovascular disease, and cancer. Additionally, a systematic review of 35 studies investigating pediatric health outcomes associated with childhood adversity provided prospective evidence of delays in cognitive development, alongside heightened risks for conditions such as asthma, infections, somatic complaints, and sleep disruptions (Oh et al., 2018). To further synthesize evidence on the health risks associated with exposure to multiple childhood adversities, K. Hughes et al. (2017) calculated risk estimates for 23 different health-related outcomes, drawing from a sample of 253,719 participants. Their analysis revealed weak associations with physical inactivity, overweight or obesity, and diabetes, moderate associations with behaviors such as smoking and heavy alcohol use, as well as with conditions like cancer, cardiovascular, and respiratory diseases. Strong associations were identified with high-risk behaviors, including sexual risk-taking, problematic substance use, interpersonal and self-directed violence, and the development of mental health disorders (K. Hughes et al., 2017).

In 2019, the financial burden of health outcomes attributable to childhood adversity was estimated at approximately USD 581 billion in Europe and USD 748 billion in North America, representing 2.7% of Europe's and 3.5% of North America's gross domestic product (Bellis et al., 2019). By calculating the population-attributable fractions (PAFs), Bellis et al. (2019) assessed how much the incidence of a certain condition would be reduced if childhood adversity were eliminated. Notably, the PAFs for mental disorders were among the highest, with childhood adversity being attributed to around 30% of anxiety cases and 40% of depression cases in North America, as well as more than 25% of both conditions in Europe (Bellis et al., 2019).

Since the 1990s, research into the relationship between childhood adversity and the risk of psychopathology has surged (Evans et al., 2013; Felitti et al., 1998). Epidemiological studies consistently demonstrate that exposure to childhood adversity drastically elevates the risk of developing both internalizing (e.g., depression, anxiety) and externalizing (e.g., disruptive behaviors, substance abuse) psychopathology, with these effects often persisting throughout the lifespan (Clark et al., 2010; McLaughlin, 2016). For example, a large-scale survey

involving 51,945 adults across 21 low-, middle-, and high-income countries estimated that roughly one-third of all mental health disorders worldwide are attributable to childhood adversity (Kessler et al., 2010). Moreover, the likelihood of developing psychopathology increases substantially with cumulative exposure to childhood adversity (S. J. Lewis et al., 2021). A recent systematic review and meta-analysis highlighted that individuals exposed to multiple childhood adversities were 3.70 times more likely to develop anxiety, 4.74 times more likely to suffer from depression, and an alarmingly 37.48 times more likely to attempt suicide compared to those without a history of childhood adversity (K. Hughes et al., 2017). Furthermore, individuals who experience multiple childhood adversities also tend to experience more persistent and severe symptoms, alongside heightened resistance to treatment (McLaughlin, Green, et al., 2010; Nanni et al., 2012). Today, the effectiveness of interventions aimed at preventing or reducing childhood adversity remains modest at best (van IJzendoorn et al., 2020). One reason for this could be the cursory understanding of the underlying mechanisms that link childhood adversity exposure to multiple forms of psychopathology.

Biological Embedding of Childhood Adversity

Disruptions in stress response systems are thought to be a central mechanism by which childhood adversity becomes biologically embedded or "gets under the skin," ultimately leading to increased vulnerability to psychopathology (Berens et al., 2017; Hertzman, 2012; McLaughlin, Sheridan, et al., 2015).

Stress is the body's coordinated physiological and psychological response to perceived endogenous or exogenous threats or demands. It disrupts homeostatic balance and strains an individual's resources and ability to cope and recover (Goldstein & McEwen, 2002; Selye, 1955, 2013). While stress can be both salubrious and deleterious, its effects are determined by the intensity and duration of the stressor. Mild, infrequent, and short-lived (i.e., positive) stress responses are not only fundamental for survival but are also an essential part of healthy development as they promote adaptation, learning, and growth. However, strong, frequent, and sustained (i.e., toxic) stress responses result in a cumulative "wear and tear" on the body, known as allostatic load, with well-established harmful effects on physical and mental health across the lifespan (Dhabhar, 2014; McEwen, 1998).

Two key neurobiological systems regulate the body's response to stress and are critical in reestablishing homeostasis. The fast-acting sympathetic nervous system (SNS) releases epinephrine (adrenaline), which quickly mobilizes metabolic resources and elicits the fight-or-flight response. Meanwhile, the slower-acting hypothalamus-pituitary-adrenal (HPA) axis triggers the adrenal-driven production of glucocorticoids (mainly cortisol). In turn, glucocorticoids

regulate HPA axis activity, contributing to neural maturation, myelination, and neurogenesis, and serving as potent anti-inflammatory and immunosuppressive agents (Auphan et al., 1995; Gunnar & Quevedo, 2007; Lupien et al., 2009). Additionally, glucocorticoids are thought to exert their prolonged effects on physiology and behavior by influencing gene expression and accelerating epigenetic aging (de Kloet et al., 1996; Marini et al., 2020; Sapolsky et al., 2000; Zannas et al., 2015).

Strong, frequent, and sustained exposure to childhood adversity can exert long-lasting programming effects on the HPA axis, leading to either hyper- or hypo-activation in response to perceived threats (Agorastos et al., 2018; Berens et al., 2017; Lupien et al., 2009; Roberts & Lopez-Duran, 2019). Both chronically elevated and suppressed glucocorticoid levels are indicative of a dysregulated HPA axis. Hyper-reactivity indicates an acquired resistance to glucocorticoid negative feedback mechanisms, leading to heightened stress sensitivity (Danese & McEwen, 2012). In contrast, hypo-reactivity indicates an exaggerated suppression of the HPA axis, resulting in diminished stress sensitivity (Lovallo, 2013). Differential patters of glucocorticoid dysregulation may arise from various factors such as type and timing of adverse experiences, genetic predispositions, current age, or existing psychopathology, with both patterns being linked to negative health and developmental outcomes (Berens et al., 2017; Danese & McEwen, 2012).

Toxic early-life stress is thought to exert its pathogenic effects particularly during sensitive periods of brain development (Berens et al., 2017). These periods of elevated brain plasticity extend into the mid-to-late 20s (Sawyer et al., 2018), with region-specific maturational changes (e.g., synaptogenesis and synaptic pruning) occurring between childhood, adolescence, and early adulthood, creating windows of heightened vulnerability (Andersen, 2003; Foulkes & Blakemore, 2018). Frontolimbic regions, including the hippocampus, amygdala, anterior cingulate cortex, and prefrontal cortex, are particularly susceptible to adverse experiences due to their dense innervation with glucocorticoid receptors and their protracted developmental trajectory (Cohodes et al., 2021; Ioannidis et al., 2020). Adversity-induced alterations in frontolimbic structure and function are believed to play a central role in the biological embedding of childhood adversity, contributing to an increased risk for psychopathology (VanTieghem & Tottenham, 2018). Critical questions remain about how the timing, severity, type, controllability, and predictability of adversity exposure influence frontolimbic development and functioning, and how these effects may, in turn, predict the risk of psychopathology (Cohodes et al., 2021).

Neurocognitive Adaptation and Poor Social Functioning Linking Childhood Adversity and Psychopathology

Neuroendocrine stress dysregulation following childhood adversity may serve short-term adaptive purposes by aiding survival in highly stressful and threatening environments, but can become maladaptive in the long-term by disrupting a range of neurocognitive and social processes, eventually increasing latent vulnerability to multiple forms of psychopathology (McCrory et al., 2019; McLaughlin et al., 2020).

The neurocognitive social transactional model of psychiatric vulnerability (Figure 1) highlights how disruptions in key stress-mediating mechanisms link childhood adversity to social stress and heightened psychopathology risk (McCrory et al., 2022). Specifically, this model proposes that adversity-induced neurocognitive adaptation in domains such as threat-, reward-, and autobiographical memory processing might contribute to a social environment characterized by more stressful interpersonal experiences (i.e., stress generation) and fewer protective social relationships (i.e., social thinning), consequently increasing vulnerability to psychopathology.

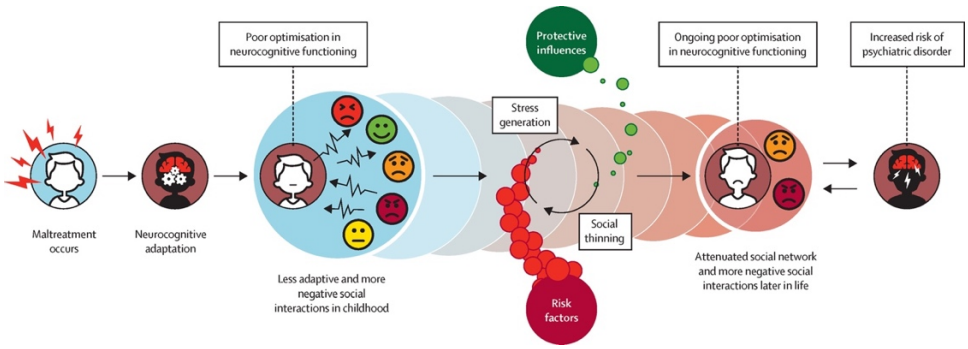

Figure 1. The neurocognitive social transactional model of psychiatric vulnerability. Reprinted from McCrory et al. (2022), with permission from Elsevier.

Disruptions in threat processing, including hypervigilance towards and avoidance of threat cues, may hold functional value in adverse environments by enhancing an individual's ability to rapidly detect and respond to potential dangers, thereby promoting safety. However, in less threatening or more normative environments, these biases may become maladaptive through facilitating social stress and increasing the risk for multiple forms of psychopathology, including conduct disorder, anxiety disorder, depression, and post-traumatic stress disorder (PTSD) (Blair & Zhang, 2020; Cisler & Koster, 2010; Etkin & Wager, 2007; Fales et al., 2008). One consistently observed pattern among individuals with childhood adversity, particularly those with threat-related experiences like physical abuse or

violence, is faster attentional engagement and altered neural responses in fronto-amygdala circuits to salient negative cues in the environment, such as angry facial expressions (McLaughlin, DeCross, et al., 2019; McLaughlin, Weissman, et al., 2019; Pollak et al., 2000). These threat processing biases may predispose them to experience interpersonal stress in ambiguous social situations, where they are more likely to respond aggressively or avoidantly to perceived social threats, which can undermine the development and maintenance of supportive social relationships (Dodge et al., 1990; Shackman & Pollak, 2014).

Disruptions in reward processing, including blunted responses to reward anticipation and receipt, may be adaptive in environments offering scares or unpredictable rewards. However, reductions in reward responsiveness may impede individuals from learning which behaviors lead to reward or from experiencing the emotional sensation of reward, which has been identified as a transdiagnostic marker of various forms of psychopathology, including depression, attention-deficit hyperactivity disorder, eating disorder, and schizophrenia (Aldridge-Waddon et al., 2020; Mackin et al., 2019; Sharma et al., 2016). Alterations in reward processing have frequently been observed among individuals with deprivation-related experiences (McLaughlin, DeCross, et al., 2019; McLaughlin, Weissman, et al., 2019; Sheridan et al., 2018). For example, deficits in approach motivation and blunted responses in fronto-striatal circuits during reward anticipation and receipt have been observed following both institutional rearing and neglect (Goff et al., 2013; Hanson, Hariri, et al., 2015). When early-life social interactions are either absent or lack rewarding qualities, long-term tendencies to trust people and expectations regarding the hedonic value of social relationships may be impacted, which will likely affect the formation of stable and supportive social networks (Pitula et al., 2017; Wismer Fries & Pollak, 2017). Additionally, a lack of motivation to follow rules and social norms may increase the risk of experiencing social stress through relational peer-victimization and bullying (Ke et al., 2022).

Disruptions in autobiographical memory processing, including overgeneral recall of single events, may serve as a coping strategy by helping individuals with childhood adversity avoid specific traumatic or distressing memories. However, alterations in how autobiographical memories are represented, recalled, and maintained have been linked to poor problem-solving abilities, negative self-representations, and an increased risk of depression and PTSD (Dalgleish & Werner-Seidler, 2014; Hallford et al., 2022; McCrory et al., 2017; Valentino et al., 2009). While adversity-specific patterns in neural responses during autobiographical memory retrieval are less well-documented, studies involving individuals with mixed adversity exposure have reported increased activation in hippocampal circuits during recall of negative, compared to positive, autobiographical memories (McCrory et al., 2017; McLaughlin, Weissman, et al.,

2019; Puetz et al., 2021). In the context of social functioning, a tendency to recall autobiographical memories in an overgeneral manner can limit access to detailed memory information necessary for navigating interpersonal challenges, such as conflicts with friends (Goddard et al., 1996). By impeding effective conflict resolution, these autobiographical memory patterns can prolong exposure to social stress and ultimately weaken social connections (Puetz et al., 2021; Sutherland & Bryant, 2008).

Together, neurocognitive adaptation following childhood adversity may offer short-term advantages in adverse environments by enhancing survival, but often result in long-term negative (social) consequences in more normative settings, increasing latent vulnerability to psychopathology (McCrory et al., 2022; McCrory & Viding, 2015). To guide prevention efforts and pinpoint specific, malleable intervention targets, future research needs to focus on identifying the neurocognitive systems most critical for predicting maladaptive social functioning and psychopathology risk in young people with childhood adversity. Having said that, not all individuals with childhood adversity are destined to develop psychopathology. Instead, some demonstrate what is referred to as resilient functioning, meaning they fare better than expected given their circumstances (Ioannidis et al., 2020). Resilient functioning following childhood adversity is thought to be facilitated by a diverse range of protective factors residing across multiple psychological, social, and neurobiological levels that help individuals adapt and recover following stress exposure (Fritz, de Graaff, et al., 2018; Ioannidis et al., 2020; Kalisch et al., 2019).

Social Stress Buffering in Young People with Childhood Adversity

One important protective factor is social support. Through alleviating the damaging psychological and neurobiological effects of (toxic) stress (Cohen & Wills, 1985; Horan & Widom, 2015), social support plays a critical role in preventing the onset and persistence of psychopathology in young people with childhood adversity (Li et al., 2022; Pine & Cohen, 2002; Trickey et al., 2012; Ungar et al., 2013).

Social stress buffering refers to the process by which the presence and availability of one or more supportive social partners, such as a primary caregiver, friend, teacher, or significant other, mitigate psychological perceptions of stress, dampen neurobiological responses to stress, and promote a faster recovery to baseline stress levels following threat exposure (Gunnar, 2017). For example, through dampening HPA axis activity and consequently lowering the release of glucocorticoids and pro-inflammatory markers into the bloodstream, social support is thought to decrease the physiological burden, or allostatic load, imposed on the body by stress exposure, thereby lowering psychopathology risk (Doan & Evans, 2011; Hennessy et al., 2009; Hostinar et al., 2014b). This

buffering effect occurs across the lifespan in diverse social settings, with its effectiveness influenced by past social experiences and the developmental stage of the recipient (Gunnar & Hostinar, 2015; Hennessy et al., 2009; Hostinar et al., 2014b). While the presence and availability of a supportive caregiver remains a potent stress buffer into late childhood, its effectiveness tends to diminish with the transition to adolescence and young adulthood as friends take on a more central role in providing emotional support and regulating stress (Gunnar & Hostinar, 2015; Gunnar et al., 2015).

Childhood is the developmental stage between infancy and adolescence, characterized by caregiver dependency and marked by significant physical, cognitive, language, and social-emotional growth (Black et al., 2017; Woodhead, 2009). Early research on social buffering of the HPA axis demonstrated that secure attachment relationships with primary caregivers can dampen stress-induced salivary cortisol increases in 2-year-olds (Gunnar et al., 1996). Similar stress buffering effects have been observed in the following years. For example, Seltzer et al. (2010) asked female children (aged 7-12 years) to complete an acute psychosocial stress task and found that following stress exposure, both physical and speech-only contact with their mothers significantly increased urinary levels of oxytocin, a neuropeptide known to inhibit stress-induced glucocorticoid secretion, while also reducing salivary cortisol levels. Research by Hostinar et al. (2015) has demonstrated that children (aged 9-11 years), but not adolescents (aged 15-16 years), exhibited caregiver buffering, as indicated by reduced salivary cortisol responses to acute psychosocial stress. Similarly, Gee et al. (2014) found evidence of maternal buffering in children (aged 4-10 years), but not in adolescents (aged 11-17 years), in the form of suppressed amygdala reactivity and improved affect-related behavioral regulation when viewing maternal compared to stranger stimuli. However, while it seems that caregivers become less central in facilitating emotion regulation and stress buffering after the onset of puberty, their presence and availability remains important, particularly for young people with childhood adversity. For example, Callaghan et al. (2019) found that both children (aged 6-10 years) and adolescents (aged 11-17 years) who had experienced institutional care prior to adoption and reported feeling more secure in their caregiver relationships exhibited reduced amygdala reactivity to caregiver cues, a protective mechanism against long-term anxiety symptoms.

The decreasing effectiveness of caregiver support in stress regulation coincides with key developmental changes typical of adolescence, including the onset of puberty, the maturation of frontolimbic circuits, and the increasing drive to seek independence from caregivers (Blakemore, 2008; Blakemore et al., 2010). Adolescence is the transitional stage between childhood and adulthood, characterized by biological growth and major social role transitions, and nowadays defined as the period between 10 and 24 years of age (Sawyer et al.,

2018). This sensitive period of social development is marked by more time spent with peers and less time spent with family (Lam et al., 2014). The developmental importance of peer companionship and intimacy becomes particularly apparent through dramatic changes in social behavior, such as the growing need for peer approval and the profound influence peers exert on decision-making, both in risky and prosocial contexts (Albert et al., 2013; Buhrmester & Furman, 1987; De Goede et al., 2009; Foulkes et al., 2018). Experiences of peer victimization during adolescence, such as peer rejection or (cyber)bullying, are prospective predictors of negative mental health outcomes (Bowes et al., 2015; Maurya et al., 2022; Prinstein & Aikins, 2004). However, in line with the friendship protection hypothesis (Boulton et al., 1999), high-quality friendship support can protect against future peer victimization and lower the risk of developing mental health problems (Bernasco et al., 2022; Cohen & Wills, 1985; Herman-Stahl & Petersen, 1996; Kendrick et al., 2012).

The availability of safe, stable, reciprocal, and supportive friendships is particularly important for young people with childhood adversity. Not only are those vulnerable young people more likely to experience peer victimization (Benedini et al., 2016; Widom et al., 2008), they are also more likely to victimize others (Fitton et al., 2020; Widom, 1989b). This cycle of victimization is thought to be fueled by adversity-induced neurocognitive adaptation, like altered threat processing, which can compromise an individual's ability to negotiate everyday social stress (Goemans et al., 2023). In turn, this heightened stress susceptibility potentiates mental health vulnerability (Gerin et al., 2019). However, just as not all young people with childhood adversity go on to develop psychopathology, not all will experience or engage in victimization. These resilient individuals likely benefit from protective factors, such as friendship support, that can help break this vicious cycle.

Friendship support has proven to buffer neurobiological stress responses in young people without childhood adversity (Gunnar, 2017; Gunnar & Hostinar, 2015). For example, two studies have demonstrated that following peer exclusion, those with higher levels of perceived social support (e.g., measured by the time spent with friends) exhibited diminished cortisol responses and lower neural activity in frontolimbic regions commonly implicated in responding to social distress (Eisenberger et al., 2007; C. L. Masten et al., 2012). Among young people with childhood adversity, research has demonstrated friendship buffering effects related to the emergence and progression of mental health problems (Powers et al., 2009; van Harmelen et al., 2016, 2021). Preliminary evidence related to friendship stress buffering in young people with childhood adversity suggests that individuals with high-quality friendship support or access to a highly responsive friend following acute psychosocial stress exhibited greater HPA axis recovery, as indicated by a faster return to baseline salivary cortisol levels (Calhoun et al.,

2014). Since disrupted neuroendocrine regulation is a marker of high allostatic load with known pathophysiological consequences (McEwen, 2000), these findings underscore the protective, stress-buffering potential of friendships. However, it remains to be investigated whether friendship support aids mental health and well-being in young people with childhood adversity through dampening psychological and neurobiological stress responses. Ultimately, a nuanced understanding of the stress-related mechanisms linking childhood adversity to later-life psychopathology, along with identifying protective factors that mitigate stress vulnerability, is essential for developing more targeted and effective prevention and intervention strategies serving young people with childhood adversity.

Dissertation Outline

This dissertation aims to enhance the mechanistic understanding of friendship stress buffering in young people with childhood adversity. Building on the neurocognitive social transactional model of psychiatric vulnerability (Figure 1; McCrory et al., 2022) and the social stress buffering framework (Gunnar, 2017), its primary goal is to identify psychological, cognitive, and neural stress-related pathways through which friendships mitigate the risk of psychopathology in this vulnerable population.

The **first part** of this dissertation addresses one of the most pervasive societal consequences of childhood adversity, commonly referred to as the cycle of victimization. Drawing on the cycle of violence hypothesis (Widom, 1989b), **Chapter 2** presents a literature review outlining the association between child maltreatment and the increased risk of perpetrating victimization both within and outside the family environment. To shed light on the mechanisms underpinning this cycle, the review detailed three maladaptive neurocognitive mechanisms that link maltreatment experiences with later-life victimization: (1) attentional bias to threat, (2) altered reward processing and feedback learning, and (3) emotion dysregulation. Importantly, the review concluded by emphasizing that not all individuals with a history of child maltreatment engage in victimization, indicating the presence of protective factors like social support that can help mitigate adversity-related vulnerabilities.

The **second part** of this dissertation focuses on the protective role of friendship support by examining psychological, cognitive, and neural mechanisms underlying friendship stress buffering in young people with childhood adversity. This part presents findings from one systematic literature review and three empirical studies: (1) the Resilience After Individual Stress Exposure (RAISE) study, (2) the Resilience after the COVID-19 Threat (REACT) study, and (3) the Towards Health and Resilience in Volatile Environments (THRIVE) study.

The **RAISE study** was a multilevel study at the University of Cambridge, UK, designed to examine psychological, cognitive, and neurobiological mechanisms and protective factors that facilitate resilient functioning in young people with childhood adversity (Moreno-López et al., 2021). Participants (N = 102, M_{age} = 22.24, 64.7% female) were recruited between August 2019 and March 2020 across Cambridgeshire, UK, from the general population through flyers, social media, and prior studies conducted by the University's Department of Psychiatry. Individuals were eligible to participate if they were aged between 16 and 26 years, able to speak, write, and understand English, had a body mass index between 18.5 and 29.9 kg/m², did not currently take medication (e.g., corticosteroids) likely to compromise data interpretation, had no MRI contraindications, and self-reported adverse experiences within the family environment before the age of 16. The RAISE study included three assessment timepoints, with data from the first two analyzed and presented in Chapter 4. At timepoint 1, participants remotely completed online self-report questionnaires assessing current (i.e., past two to four weeks) mental health and well-being, perceived friendship support, and retrospective childhood adversity (N = 102, baseline sample). At timepoint 2, on average one month later, participants attended in-unit assessments at Addenbrooke's Hospital in Cambridge, UK (n = 62, neuroimaging sample). This visit included, among other measures, functional magnetic resonance imaging (fMRI) during which participants completed the Montreal Imaging Stress Task (MIST) (Pruessner et al., 2008). The MIST is a widely used and well-validated acute psychosocial stress paradigm for fMRI that involves a mental arithmetic task performed under time constraints, with an artificially induced failure component and negative verbal feedback delivered by a trained member of the research team. The neuroimaging sample was smaller than the baseline sample due to a University-wide suspension of laboratory research activities in March 2020 in response to the COVID-19 outbreak. However, both groups did not significantly differ in key characteristics, such as age, gender, childhood adversity, or friendship quality. For a comprehensive description of the full study procedure, inclusion and exclusion criteria, and a complete list of all measures, see Moreno-López et al. (2021).

The **REACT study** was a longitudinal follow-up initiated after the COVID-19 outbreak to prospectively examine pandemic-related changes in psychosocial functioning among all RAISE participants (N = 102) who were recruited between August 2019 and March 2020 and had consented to be recontacted for future studies (A. J. Smith et al., 2021). Participants were recruited remotely for three follow-up assessment timepoints. The first follow-up took place during the first national lockdown in the UK (n = 79, April to May 2020), the second during a period of eased restrictions (n = 77, July to August 2020), and the third during another phase of heightened restrictions (n = 73, October to November 2020). Despite retention challenges, participants who completed follow-ups did not

differ significantly from the pre-pandemic baseline sample in key characteristics. At each follow-up, participants completed online self-report questionnaires, assessing variables such as current (i.e., past two weeks) mental health, perceived friendship support, and perceived stress. For a comprehensive description of the full study procedure and a complete list of all measures, see A. J. Smith et al. (2021).

The **THRIVE study** is an ongoing longitudinal study at Leiden University, the Netherlands, also designed to investigate psychological, cognitive, and neurobiological mechanisms and protective factors that facilitate resilient functioning in young people with childhood adversity. Participant recruitment commenced in October 2022 and involves outreach to the general population across the Netherlands through flyer distribution at schools and universities, general practitioner practices, shops, libraries, hospitals, out-patient care facilities, and social media. Eligible participants are aged 18 to 24 years, able to speak, write, and understand Dutch, self-report adverse experiences within or outside the family environment before the age of 18, and have not experienced severe depressive symptoms or suicidal thoughts in the two weeks prior to eligibility screening. Due to the ongoing nature of the study, Chapter 6 presents cross-sectional findings from the first 100 participants (M_{age} = 21.23, 79.0 % female) who completed the initial two (of seven) assessment timepoints. At timepoint 1, participants remotely completed online self-report questionnaires assessing currently perceived friendship support and retrospective childhood adversity. At timepoint 2, on average one month later, participants attended in-unit assessments at the Leiden University Medical Center in Leiden, the Netherlands. This visit included, among other measures, the completion of online self-report questionnaires assessing current (i.e., past two weeks) mental health and perceived stress, as well as an adapted version of the Autobiographical Memory Task (J. M. Williams & Broadbent, 1986), asking participants to recall a memory of a situation or experience with a friend prompted by a positive or negative cue word. A protocol paper providing a detailed description of the study procedure, inclusion and exclusion criteria, and a complete list of all measures is expected to be published soon.

Before outlining the insights gained through the three empirical studies, **Chapter 3** presents a pre-registered systematic literature review that investigated whether greater friendship support reduces neural stress responses in young people with childhood adversity. Building on a growing body of evidence demonstrating the protective effects of friendship support on youth mental health following childhood adversity (van Harmelen et al., 2016, 2021), this review searched for empirical studies published in English through December 2021, involving young people (aged 10-24 years) with childhood adversity, and measures of friendship support and neural stress responses assessed using neuroimaging techniques.

Utilizing cross-sectional behavioral and neuroimaging data from the RAISE study, **Chapter 4** outlines whether greater friendship support predicts reduced neural stress responses in young people with childhood adversity. Specifically, this neuroimaging study examined three hypotheses: (1) whether more severe childhood adversity predicts lower friendship support, which in turn predicts poorer mental health and well-being; (2) whether acute psychosocial stress induced by the MIST elevates state anxiety and neural activity in seven predefined frontolimbic regions of interest (ROIs); and (3) whether greater friendship support predicts reduced frontolimbic ROI reactivity to stress. These hypotheses were tested using both a cumulative risk and dimensional approach, with the expectation that more severe threat-related adversity would be associated with heightened frontolimbic ROI reactivity to stress.

Utilizing longitudinal behavioral data from the REACT study, **Chapter 5** outlines whether greater friendship support predicts reduced mental health symptoms in young people with childhood adversity, both before and at three timepoints during the COVID-19 pandemic. Specifically, this prospective longitudinal study examined three hypotheses: (1) whether the COVID-19 outbreak predicts an overall increase in anxiety and depressive symptoms, along with a decrease in friendship support, with these trends expected to be exacerbated during lockdown periods; (2) whether more severe childhood adversity predicts reduced friendship support and heightened mental health symptoms during the pandemic; and (3) whether greater friendship support predicts fewer mental health symptoms. Additionally, the study explored perceived stress as a potential mechanism linking friendship support to mental health outcomes during the pandemic.

Utilizing cross-sectional behavioral data from the THRIVE study, **Chapter 6** outlines whether greater friendship support predicts autobiographical friendship memory specificity in young people with childhood adversity, as well as its associations with perceived stress and mental health. Specifically, this study examined three hypotheses: (1) whether greater friendship support predicts greater specificity of positive autobiographical friendship memories, lower perceived stress, and fewer depressive symptoms; (2) whether greater specificity of positive memories predicts lower perceived stress and fewer depressive symptoms; and (3) whether lower perceived stress predicts fewer depressive symptoms. To account for potential valence-specific effects, both positive and negative memory associations were analyzed.

This dissertation concludes with an executive summary and general discussion, synthesizing key findings across all chapters, outlining limitations, and proposing directions for future research (**Chapter 7**).