Friendship stress buffering in young people with childhood adversity

König, M.

Chapter 3

The Importance of Friendships in Reducing Brain Responses to Stress in Adolescents Exposed to Childhood Adversity: A Pre-Registered Systematic Review

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Abstract
Up to 50% of all children and adolescents growing up worldwide are exposed to at least one form of childhood adversity (CA), which is one of the strongest predictors for later-life psychopathology. One way through which CA confers such vulnerability in later-life is through increased sensitivity to and likelihood of social stress. A growing body of research demonstrates the positive impact of adolescent friendship support on mental well-being after CA, however, the mechanisms that may underlie this relationship are unknown. Neurobiological models of social buffering suggest that social support can reduce perceptions, reactions, and physiological responses to and after stress. Therefore, this pre-registered, systematic literature search examined whether friendships reduce neural stress responses in adolescents with CA.

Keywords: friendship buffering, social support, neural stress mechanisms, childhood adversity, adolescence, systematic review.

Introduction

Up to 50% of all children and adolescents growing up worldwide are exposed to at least one form of childhood adversity (CA; e.g., abuse, neglect, bullying, or poverty) (Bellis et al., 2014; McLaughlin, 2016). CA is a strong predictor of later-life mental health and interpersonal problems. One way through which CA confers such vulnerability is through increased sensitivity to and likelihood of interpersonal stress (e.g., peer relationship problems) (Humphreys et al., 2016; van Harmelen et al., 2014, 2016). As such, to improve well-being, it is imperative that stress vulnerability is reduced in young people with CA.

Safe, stable, and nurturing social relationships can help reduce perceptions, reactions, and physiological responses to and after stress (Gunnar, 2017). Friendships may be a particularly important support source in adolescence, as this is a time when young people start to form more stable, intimate, and reciprocal peer relationships (Orben et al., 2020). Friendship support has indeed been found to improve mental well-being in young people with CA (van Harmelen et al., 2016, 2021). However, it is unknown whether friendship support aids mental well-being through reducing stress responses in these individuals. Therefore, we performed a pre-registered, systematic literature search to examine whether friendship support reduces brain responses to stress in adolescents with CA (see Figure 1).

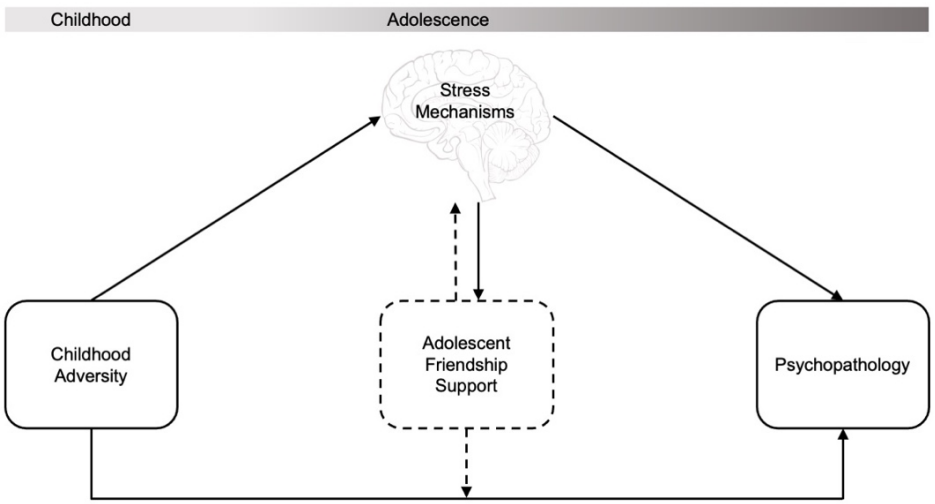

Figure 1. Friendship buffering effects on brain responses to stress in adolescents with CA. Adolescent friendship support may help reduce (or buffer) neural stress responses (dashed lines) that are thought to aid psychopathology in young people with CA (solid lines).

Neurobiological Stress Mechanisms Linking CA and Psychopathology

Prolonged stress exposure early in life can disrupt the development of psychological and neurobiological processes and thereby increase vulnerability to psychopathology (Y. Chen & Baram, 2016). In humans, CA can impair the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis; a key stress response system that gets activated when homeostasis (i.e., the body's tendency to maintain a stable internal environment) is threatened. The HPA axis is responsible for producing stress hormones (e.g., cortisol), also known as glucocorticoids (Gunnar et al., 2019; Lupien et al., 2009). Glucocorticoids are potent anti-inflammatory as well as immunosuppressive agents and are important for healthy brain development due to their involvement in neural maturation, myelination, and neurogenesis (Auphan et al., 1995; Lupien et al., 2009). In the context of CA, sustained HPA axis activation can lead to chronically elevated levels of glucocorticoids in the brain and altered frontolimbic development and functioning (Cohodes et al., 2021; McEwen, 2012). Due to their dense innervation with glucocorticoid receptors, brain regions like the hippocampus, amygdala, anterior cingulate cortex, or prefrontal cortex may be particularly impacted resulting, for example, in dysfunctional social information- and emotional processing (Arnsten, 2015; McLaughlin et al., 2020; Tottenham & Sheridan, 2010). According to the theory of latent vulnerability, alterations to these mechanisms may be adaptive in the short-term to support survival in highly stressful and threatening environments. However, in the long-term, such recalibration of the stress system can become maladaptive (McCrory et al., 2019). For example, in the context of an abusive home environment, it may be adaptive to rapidly detect threats (e.g., angry facial expressions). However, in less threatening environments this amygdala-supported attentional bias to threat may aid an over-attribution of hostile intentions to others' action, possibly eliciting preemptive (aggressive or avoidance) behavior (Heuer et al., 2007; N. V. Miller & Johnston, 2019). Indeed, such attentional biases were predictive of future onset of internalizing and externalizing problems in young people with CA (Shackman & Pollak, 2014) and were linked to reduced social interactions and greater difficulties with peers (Humphreys et al., 2016). Forming and maintaining friendships, defined as voluntary, reciprocal, and nurturing relationships, requires social-emotional competence (McCrory et al., 2019), which relies in part on neurocognitive mechanisms (e.g., emotion perception and regulation) known to be altered in adolescents with CA (Benedini et al., 2016; McCrory et al., 2019). Consequently, through this mechanism, young people with CA may be more vulnerable and more likely to experience social stress (i.e., stress generation; McCrory et al. (2019)). CA is therefore thought to shape neurodevelopment in a way that increases vulnerability to social stress (J. Kim & Cicchetti, 2009; McCrory et al., 2019; McLaughlin et al., 2020).

Social Buffering of Neurobiological Stress Responses across Development

Social buffering describes the phenomenon in which a social partner can attenuate acute physiological stress responses (Gunnar, 2017). This leads to a reduction in the release of glucocorticoids and proinflammatory markers into the bloodstream (Hostinar et al., 2014a; R. M. Sullivan & Perry, 2015). In humans, this decreased allostatic load (i.e., the physiological impact of stress on the body) may help protect against the emergence of psychopathology (S. Cohen & Wills, 1985; McLaughlin et al., 2020). Indeed, trauma exposed young people with high levels of social support are less likely to develop psychopathology (Trickey et al., 2012).

Social buffering occurs throughout the lifespan and its effectiveness is influenced by previous social experiences, as well as the developmental stage of the recipient (Hennessy et al., 2009). During early childhood, the caregiver is the most potent stress buffer. Animal models have demonstrated that maternal presence can attenuate glucocorticoid release and block amygdala-dependent threat learning in rodent pups (Raineki et al., 2014; R. M. Sullivan & Perry, 2015). Similarly, in humans, maternal availability after a social evaluative performance stressor was found to facilitate greater oxytocin release, a neuropeptide capable of inhibiting glucocorticoid secretion in response to stress, as well as a more rapid decrease and lower levels of peak cortisol in children (Seltzer et al., 2010). Across social species, high-quality caregiving, characterized by predictable caregiving that signals safety, can improve the effectiveness of social buffering (Ainsworth et al., 1974; Gee & Cohodes, 2021). In humans, high-quality caregiving modulates children's frontolimbic circuitry and contributes to healthy socioemotional functioning (Gee & Cohodes, 2021). For example, greater feelings of child-reported security in the caregiver-child attachment relationship buffers amygdala reactivity, enhances affective behavior, and mental health (Callaghan et al., 2019; Gee et al., 2014).

While caregivers remain potent stress buffers throughout childhood, evidence suggests that their effectiveness diminishes with the transition to adolescence (Gee et al., 2014; Hostinar et al., 2015). One potential mechanism proposes that with the maturation of frontolimbic circuitry caregivers lose their active role in facilitating emotion regulation and buffering amygdala reactivity (Gee & Cohodes, 2021; Gee et al., 2014; Hostinar et al., 2015). This makes space for other attachment figures to take over the stress-alleviating role of social support. At the same time, adolescents learn to navigate the world more independently and start to increasingly form and maintain emotionally intimate peer relationships (Orben et al., 2020). Hence, peers take on a more central role in social-emotional buffering (Gee & Cohodes, 2021).

Adolescent friendship support is a potent protective factor, capable of buffering threat-related processing (see Gunnar (2017) for review). Specifically, adolescents with heightened levels of perceived social support (e.g., measured through the time spent interacting with friends) had diminished cortisol responses and lower neural activity in brain regions commonly associated with social distress following social exclusion (Eisenberger et al., 2007; C. L. Masten et al., 2012), providing initial evidence that adolescent friendships may buffer neural stress responses in young people without CA (Eisenberger et al., 2007). However, it is yet unknown whether friendship support similarly buffers neural stress responses in vulnerable adolescents with CA.

Do Friendships Reduce Neural Stress Responses in Adolescents with CA?

While there is a growing body of research demonstrating the positive impact of adolescent friendship support on mental well-being after CA (Fritz, Stretton, et al., 2020; van Harmelen et al., 2016, 2021), very little is known about the neural mechanisms that aid this relationship. Therefore, we performed a pre-registered, systematic literature review to examine whether friendship support buffers neural stress responsivity in adolescents with CA (Prospero: CRD42021233949).

Systematic Review: Study Selection and Data Extraction

In accordance with the PRISMA guidelines (Page et al., 2021), we searched for empirical studies (peer-reviewed articles, proceedings papers, and conference papers) published in English and involving human subjects by using internet databases (Web of Science Core Collection, PubMed, and PsycINFO) through December 2021.

We included studies assessing friendships and neural stress responses in adolescents with CA. Specifically, we included studies in which at least a portion of the adolescent sample (sample mean age 10-24) had experienced or reported a history of CA. CA was defined as any event assessed prior to the age of 18, which is "likely to require significant adaption by an average child and that represent[s] a deviation from the expectable environment" (McLaughlin, 2016, p. 363), such as abuse, neglect, or bullying. Friendships had to be assessed between the (sample mean) age of 10-24 and were defined as self- or other-reported, subjective or objective peer relationships, excluding support from family, pets, community ties, or co-workers. Measures of neural stress responses needed to be induced (e.g., stress exposure or negative feedback) in the lab, and assessed using neuroimaging techniques (e.g., fMRI or EEG).

These categories were included in search terms encompassing friendship support, study population, neural domains, CA, and stress exposure (see Table S1 for all search terms used). To identify studies missed in this targeted search, we

performed backward reference searches, and used Google Scholar for forward searching.

A total of 6,260 articles were identified. After removing duplicates, two independent reviewers screened titles, abstracts, and keywords of 4,297 articles based on the PI(C)OS concept: population (P; adolescents between the age of 10-24 (sample mean age) with CA (assessed prior to the age of 18)), intervention (I; friendships assessed between the age of 10-24 (sample mean age)), outcome (O; neural stress mechanisms), and study design (S; empirical study) (Liberati et al., 2009). This screening resulted in adequate inter-rater reliability of Kappa = .58, disagreement was resolved through discussion. Next, 66 full-text articles were selected and subsequently assessed for eligibility, however, only two articles matched all search criteria (Kappa = .79) (Figure 2). Therefore, we allowed stress responses in any neurobiological system (incl. endocrine and sympathetic nervous system) and included two additional studies. For a detailed summary of all excluded studies see Tables S2-6. A risk of bias (quality) assessment was performed for the four included studies, in which studies could score one point for each quality marker they met (e.g., "Is the sample representative of the defined population?"). The overall quality score (QA score) for each study was calculated by adding up all nine items (see Table S7 for all assessment questions).

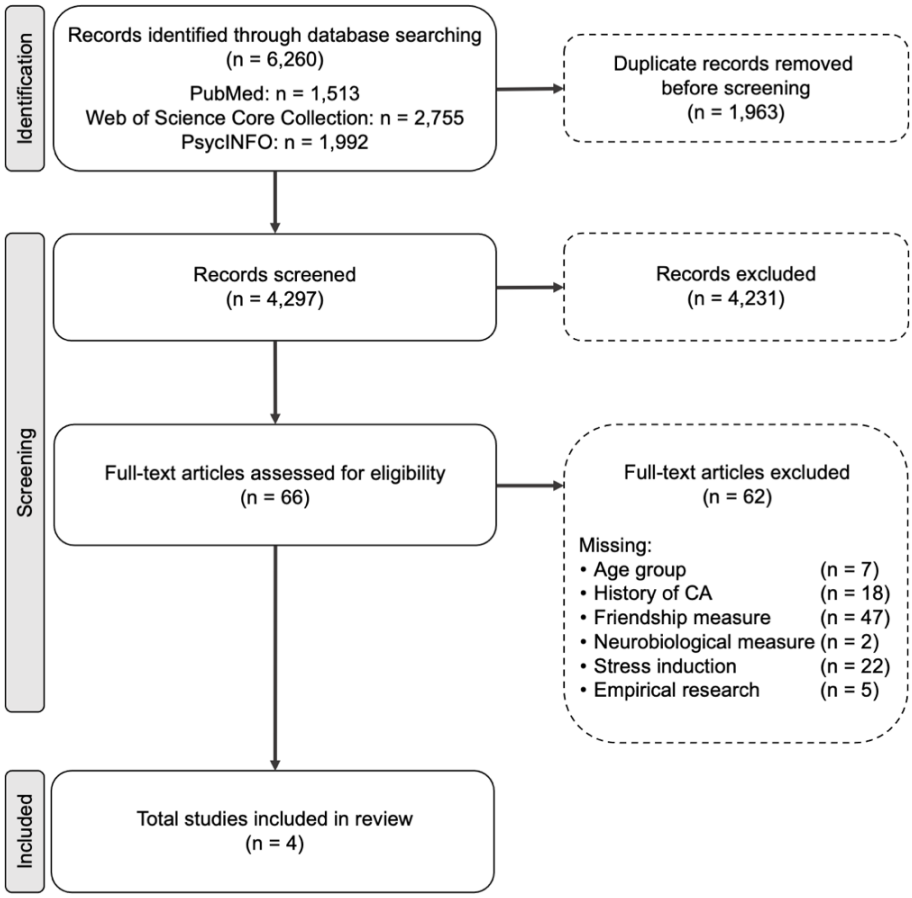

Figure 2. *PRISMA flow diagram.* Adapted from (Page et al., 2021).

Results

This pre-registered, systematic review identified four eligible studies (Fritz, Stretton, et al., 2020; Kelly et al., 2015; Negriff et al., 2020; Alva Tang et al., 2021) (see Figure 2). Only two of those studies did directly test whether friendships buffer neurobiological stress responses in adolescents with CA (Fritz, Stretton, et al., 2020; Tang et al., 2021). Tang et al. (2021) showed that high-quality friendships at age 12 can buffer the indirect effect of maladaptive stress physiology (blunted sympathetic nervous system reactivity to social rejection feedback) on peer problems at age 16 in 217 adolescents (136 with CA) who had been institutionalized. In contrast, Fritz, Stretton, et al. (2020) found that friendship support at ages 14 or 17 was not associated with affective behavioral or neural responses to social rejection at age 18 in a small sample of 55 adolescents (26 with CA). Although, adolescents with CA reported more friendship support at age 14, suggesting a particularly well-functioning sample with possibly normalized stress responses. Indeed, Schweizer et al. (2016) reported enhanced emotion regulation

capacity in the same cohort of adolescents with CA, perhaps obscuring the ability to comprehensively examine friendship stress buffering effects.

The remaining two studies included in the review did not directly test the model of interest (Kelly et al., 2015; Negriff et al., 2020). Kelly et al. (2015) found that adolescents (aged 10-14) with documented maltreatment experiences displayed increased emotional reactivity, an attentional bias away from threat, and reduced gray matter volume (GMV) in the left medial orbitofrontal cortex (mOFC), a brain region implicated in empathic, social functioning. In addition, reduced GMV in the left mOFC mediated the relationship between maltreatment and peer relationship problems providing support for neural stress generation and mechanisms in adolescents with CA. Similarly, Negriff et al. (2020) found that 10-year-old adolescents with CA reported a smaller perceived friendship support network and showed blunted cortisol responses to social stress. However, in both studies it was not specifically tested whether friendship support or network characteristics (size or interconnections) were associated with reduced neurobiological stress responses.

These findings add to studies that were excluded from the current review due to missing search criteria (summarized in Tables S2-6). For example, studies investigating friendship stress buffering in individuals without CA demonstrated that adolescents who spent more time with friends showed reduced neural activity (dACC and anterior insula) during social exclusion (C. L. Masten et al., 2012). Whereas adults with below average levels of perceived social support showed a positive correlation between threat-related amygdala reactivity and trait anxiety (Hyde et al., 2011).

Moreover, three excluded studies supported the notion of friendship buffering on neurobiological mechanisms, despite not investigating stress responses (Gu et al., 2020; Malhi et al., 2020; Reid et al., 2021). First, Reid et al. (2021) found that the quality of social support, but not previous institutionalization experiences, predicted changes in diurnal cortisol patterns across early adolescence. Specifically, higher levels of social support were associated with lower bedtime cortisol levels. Second, Gu et al. (2020) tested adolescents orphaned by parental HIV/AIDS who displayed decreased cortical resting state activity (elevated theta-to-beta ratio) in fronto-central regions, which was also associated with greater learning and behavioral problems as well as difficulties making friends. Similarly, Malhi et al. (2020) showed that adolescents (12-18 years) with severe emotional trauma had smaller left hippocampal volumes as well as less perceived social support from friends, family, and significant others, compared to individuals with minimal trauma exposure. In addition, the former two studies (Gu et al., 2020; Malhi et al., 2020) lend further support to the stress generation idea through which friendship support may also be less available to young people with CA.

Paper	*N*	Age (years)	Adversity	Friendship Support	Neuro-biology	Stress	Main Findings	QA Score
Fritz, Stretton, et al. (2020)	Total: 55 CA: 26 Control: 29	Three timepoints: 14, 17, 18 *Scanning at T_3*	Intrafamily adverse events CAMEEI performed with primary caregiver	Perceived friendship support CFQ	Brain function	Social feedback task	CA predicted higher levels of perceived friendship support at age 14, which was associated with perceived friendship support at age 17. However, friendship support at either age did not mediate the link between CA and affective behavioral or neural (AI and dACC) responses to social rejection.	7

Kelly et al. (2015)	Total: 122 CA: 62 Control: 60	10-14	Maltreatment Child Protection Service records	Perceived access of support from others Perceived sense of relatedness scale of the RSCA	Brain structure	Threat process-ing task	Maltreated adolescents showed increased behavioral threat reactivity, greater peer problems, which were partly mediated by reduced GMV in the left mOFC as well as no group specific differences in perceived friendship support. However, it was not specifically tested whether friendship support was associated with reduced mOFC GMV, emotional reactivity, or changes in attentional threat bias in this sample.	6

Negriff et al. (2020)	Total: 303 CA: 303 Control: 151	Four timepoints: 10, 12, 14, 18	Maltreatment Child Protection Service records	Perceived social support (incl. friendships) Social Network Interview; CSSQ; MOS-SS	Salivary cortisol, salivary alpha amylase	TSST	At age 10, maltreated adolescents not only reported a smaller perceived friendship support network, compared to the age-matched non-maltreated comparison group, they also showed a blunted cortisol response to social stress, which was especially pronounced for adolescents, who experienced physical or sexual abuse. However, it was not specifically investigated whether the size and interconnections of the friendship support network were associated with lower cortisol responses to social stress.	5

Tang et al. (2021)	Total: 217 CA: 136 Control: 135	Two timepoints: 12, 16	Institutional rearing Bucharest Early Intervention Project	Friendship quality	Sympathetic nervous system reactivity	Social evaluation task	High-quality friendships at age 12 can buffer the indirect effect of blunted SNS reactivity to social rejection feedback on peer problems at age 16 following early institutionalization.	8

Table 1. Summary of studies included in the systematic review. Summary of four studies included in the systematic review. Abbreviations: CAMEEI = cambridge early experiences interview; CFQ = cambridge friendship questionnaire; CA = childhood adversity; AI = anterior insula; (d)AAC = (dorsal) anterior cingulate cortex; QA Score = quality assessment score; RSCA = resiliency scale for children and adolescents; GMV = gray matter volume; (m)OFC = (medial) orbitofrontal cortex; CSSQ = child social support questionnaire; MOS-SS = MOS social support survey; TSST = trier social stress test; T_3 = Timepoint three; SNS = sympathetic nervous system.

Discussion

This pre-registered, systematic review identified only four studies that could have examined whether friendship support buffers neurobiological stress responses in adolescents with CA (Fritz, Stretton, et al., 2020; Kelly et al., 2015; Negriff et al., 2020; Tang et al., 2021). One study found support for friendship stress buffering in a large sample of previously institutionalized adolescents (Tang et al., 2021), whereas two studies did not directly test this model (Kelly et al., 2015; Negriff et al., 2020), and another was limited by an underpowered sample of well-functioning adolescents with mild to moderate CA (Fritz, Stretton, et al., 2020). Previous research (incl. Negriff et al. (2020)) classified individuals with CA exposure as more sensitive and likely to experience interpersonal stress due to compromised social-emotional functioning (Benedini et al., 2016; Humphreys et al., 2016; Kelly et al., 2015; McCrory et al., 2019). Through this mechanism, it is suggested that friendship support may also be less available to young people with CA. However, Kelly et al. (2015) and Fritz, Stretton, et al. (2020) demonstrated that adolescents with CA can have normative or even increased levels of friendships support. This is promising, considering that greater friendship support has been proven to promote mental well-being in this population (van Harmelen et al., 2021) as well as reduce neurobiological responses to social stress in adolescents without CA (Eisenberger et al., 2007; C. L. Masten et al., 2012). Given that friendship stress buffering was only studied in two samples, future research is clearly needed to investigate whether friendships aid mental well-being through reducing neurobiological stress responses in adolescents with CA.

Future research should explore the heterogeneity in CA exposure as well as the types of assessment. For example, a dimensional approach could be used to conceptualize complex CA experiences along distinct dimensions of threat and deprivation in order to capture their impact on neurobiological stress mechanisms (McLaughlin & Sheridan, 2016). However, whether this approach allows the field to ultimately advance from cumulative measures of risk remains to be further investigated (see Pollak & Smith (2021)). Furthermore, previous empirical and meta-analytic evidence has confirmed that prospective documentation (objective) and retrospective self-report (subjective) measures of CA identify individuals with differential neural outcomes and psychopathological risk trajectories (Baldwin et al., 2019; Danese & Widom, 2020). Specifically, understanding and measuring variability in subjective life experiences appears crucial for identifying maladaptive neurobiological stress mechanisms linking CA exposure and risk of psychopathology.

Differential dimensions of friendships (e.g., intimacy or support network size) as well as developmental differences should also be considered. For example, (A. M. Smith et al., 2009) showed that the degree of psychological closeness between same-sex adolescent stranger pairs modulates cortisol responses during a social

stress task. Moreover, Hostinar et al. (2015) showed that parental support becomes less effective in reducing cortisol stress responses (i.e., HPA reactivity) from childhood to adolescence. Hence, future studies should include well powered samples to allow for the investigation of heterogeneity of CA and its assessments as well as friendship dimensions and developmental timing on friendship stress buffering in young people with CA.

In sum, this systematic review identified only two studies that specifically tested whether friendship support buffers neural stress responses in adolescents with CA. Both studies provided divergent evidence for the stress buffering role of friendship support, which is why future research is clearly needed to investigate whether friendships reduce stress vulnerability in young people with CA.

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Declaration of Competing Interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Information

Search Terms	
Search category: title, abstract & keywords	
	(friend* OR peer* OR "social support")
AND	(child* OR adolescen* OR teen* OR youth* OR "development")
AND	("brain" OR "neural" OR "grey matter" OR "white matter" OR structur* OR function* OR neurobiolog* OR "fmri" OR "mri" OR "diffusion mri" OR "dti" OR "eeg" OR "tms" OR "diffusion tensor imaging" OR "transcranial magnetic stimulation" OR "electroencephalography" OR "magnetic resonance imaging" OR "functional magnetic resonance imaging")
AND	(advers* OR maltreat* OR mistreat* OR abuse* OR assault* OR molest* OR neglect* OR victim* OR orphan* OR institutional* OR trauma* OR "deprivation" OR "early life stress" OR "corporal punishment" OR "domestic violence" OR "witnessing intimate partner violence" OR "family conflict" OR "abandonment" OR "physical discipline" OR "bullying")
AND	(stress* OR "exclusion" OR "rejection" OR "negative feedback" OR "peer pressure" OR "distress")
Documents	
	peer-reviewed articles, proceedings papers and conference papers
Databases	
	Web of Science Core Collection, PubMed, PsycINFO

Table S1. Search terms and databases used for the systematic review. Overview of search terms and databases used for the pre-registered, systematic review (Prospero: CRD42021233949). Five categories were included in the search strategy to encompass friendship support, study population, neural domains, CA, and stress exposure. In line with the PRISMA guidelines (Page et al., 2021), databases were searched for empirical studies published in English and involving human subjects for all available years through December 2021.

Paper	*N*	Age (years)	Adversity	Friendship Support	Neuro-biology	Stress	Main Findings
Kiefer et al. (2021)	29	*M* = 13.5	Peer victimization	-	Brain function	Cyberball	Adolescents with a history of chronic peer victimization showed higher neural activity in frontal brain areas (sg/pgACC, left IFG, and dlPFC) during social exclusion. In addition, this exclusion-specific signal increase was positively related to the severity of prior victimization experience.
McIver et al. (2018)	45	17-19	Peer victimization	-	Brain function	Cyberball	Adolescents with a history of peer victimization showed heightened neural activity (left amygdala, left parahippocampal gyrus, left inferior frontal operculum, and right fusiform gyrus) during social exclusion.
McIver et al. (2019)	45	*M* = 17.7	Peer victimization	-	Brain function	Cyberball	In adolescents with CA, functional connectivity between the left amygdala-ACC and left amygdala-mPFC was greater during social inclusion than exclusion, which also predicted a greater risk for depressive symptoms.

Puetz et al. (2014)	51	7-14	Early separation experiences	-	Brain function	Cyberball	During social exclusion, individuals with CA showed increased affective behavioral and threat-related neural responses (middle temporal gyrus, thalamus, and ventral tegmental area) as well as reduced activity in brain regions implicated in affect regulation (dlPFC and dACC).
Rudolph et al. (2016)	47	*M* = 15.46	Peer victimization	-	Brain function	Cyberball	Adolescents with a history of peer victimization showed higher neural activity (dACC) during social exclusion, which was also associated with internalizing symptoms.
van Harmelen et al. (2014)	46	*M* = 19.2	Emotional maltreatment	-	Brain function	Cyberball	Severity of maltreatment was positively associated with increased neural responsivity (dorsal mPFC) to social exclusion.
Will, van Lier, et al. (2016)	44	12-15	Chronic peer rejection	-	Brain function	Cyberball	Adolescents with a history of chronic peer rejection showed higher neural activity (dAAC) during social exclusion.

Jarcho et al. (2019)	47	*M* = 10.91	Peer victimization	-	Brain function	Social evaluation paradigm	During unpredictable peer evaluation, adolescents with more severe peer victimization experiences showed greater wariness, which was linked to stronger neural responses (right amygdala).
Laceulle et al. (2017)	141	Two timepoints: 16, 19	Childhood adversity	-	Endocrine measures	TSST	Adolescents with a history of social defeat showed increased basal cortisol levels and decreased reactions to the stress task from age 16 to 19, compared to peers with a history of loss/illness as well as those with no CA.
Oppenheimer et al. (2020)	36	11-16	Peer victimization	-	Brain function	Social acceptance & rejection task	Adolescents with greater severity of suicidal ideation exhibited increased neural activation (right anterior insula) during social rejection as well as reported high levels of peer victimization or EMA-measured daily negative social experiences.

Pegg et al. (2019)	231	*M* = 18.16	Lifetime stress exposure	-	ERPs	Island Getaway task (Vote to accept/ reject peers & receive acceptance/ rejection feedback)	Adolescents with greater lifetime social stress exposure and reduced social reward responsiveness showed greater depressive symptoms.
Puetz et al. (2016)	41	10-14	Maltreatment	-	Brain function	Social rejection-themed emotional Stroop task	Maltreated adolescents displayed hypoactivation to rejection cues in regions previously implicated in abuse-related posttraumatic stress disorder (e.g., left anterior insula).

Table S2. Excluded studies examining the impact of childhood adversity on neurobiological stress mechanisms. Twelve articles investigating the impact of childhood adversity on neurobiological stress mechanisms were excluded from the review due to missing friendship support measures. Most studies used social rejection paradigms and found that adolescent with childhood adversity showed greater affective behavioral and neural responsivity during social exclusion. However, these studies were unable to investigate whether friendships buffer neurobiological stress responses. Abbreviations: (sg/pg)ACC = (sub/perigenual) anterior cingulate cortex; IFG = inferior frontal gyrus; (dl)PFC = (dorsolateral) prefrontal cortex; CA = childhood adversity; (d)ACC = (dorsal) anterior cingulate cortex; (d)(m)PFC = (dorsal) (medial) prefrontal cortex; TSST = trier social stress task; EMA = ecological momentary assessment; ERPs = event-related potentials.

Paper	*N*	Age (years)	Adversity	Friendship Support	Neuro-biology	Stress	Main Findings
Baddam et al. (2016)	46	8-13	-	Best friend pairs *Note: friendship support was not directly assessed*	ERPs	Cyberball	Youth rejected by a stranger showed greater brain responses (P2 and positive slow wave ERP) compared to being rejected by a friend.
C. L. Masten et al. (2012)	21	*M* = 17.77	-	Time spent with friends outside of school each day for 2 weeks	Brain function	Cyberball	Adolescents who spent more time with friends showed reduced neural activity (dACC and anterior insula) during social exclusion.

Table S3. Excluded studies examining friendship buffering of neurobiological stress responses in adolescents without childhood adversity. Two articles investigating friendship buffering of neurobiological stress responses in adolescents were excluded from the review due to a sample without a recorded history of childhood adversity. Only one study did directly assess friendship support and provided initial evidence that friendships may buffer neural stress responses in adolescents without childhood adversity. Abbreviations: ERPs = event-related potentials; (d)ACC = (dorsal) anterior cingulate cortex.

Paper	*N*	Age (years)	Adversity	Friendship Support	Neuro-biology	Stress	Main Findings
Learning							
Gu et al. (2020)	128	9-17	Orphaned by parental HIV/AIDS	Ability to make friends (i.e., peer social skills)	ERPs	-	Adolescents orphaned by parental HIV/AIDS displayed an increased theta-to-beta power ratio (an EEG marker of decreased cortical activity) in fronto-central regions linked with greater learning and behavioral problems as well as difficulties making friends. However, the authors did not further investigate whether reduced peer social skills impacted the quality of already existing friendships and whether those friendships were associated with reduced cortical resting state activity.
Silvers et al. (2016)	89	7-16	Institutional rearing	-	Brain function	Aversive learning task	Youth who experienced prior institutionalization specifically recruited the hippocampus during aversive learning. Also, connectivity between the hippocampus and PFC prospectively predicted a reduction in anxiety symptoms 2 years later.

Reward Processing

Casement et al. (2014)	120	Two timepoints: 11/12, 16	Peer victimization & low parental warmth	-	Brain function	-	Adolescents who experienced peer victimization showed reduced neural responses (mPFC) to potential rewards, which also mediated the association with depressive symptoms.
Eckstrand et al. (2019)	46	14-18	Peer victimization	-	Brain function	Social reward task	Sexual minority adolescents reported greater interpersonal depressive symptoms and showed blunted neural responses (right mPFC, left anterior insula, right temporoparietal junction) to social, but not monetary, reward.
Ethridge et al. (2018)	61	18-25	Peer victimization	-	ERPs	Doors task (forced choice guessing task)	Adolescents with past-year relational, but not physical, victimization experiences showed blunted brain responses to rewards.
Rappaport et al. (2019)	56	*M* = 18.05	Peer victimization	-	ERPs	Social reward task	Adolescents exposed to peer victimization showed reduced brain responses (reward positivity) to social than monetary rewards.

Emotion Processing

Gerin et al. (2019)	196	*M* = 19.49	Childhood adversity	-	Brain function	Face-matching paradigm	Adolescents with CA showed increased baseline neural reactivity (amygdala) to threat and had a greater likelihood of reporting elevated post-baseline exposure to major stressful life events as well as internalizing symptoms at follow-up.
Loth et al. (2014)	1445	12-15	Stressful life events	-	Brain function	Angry faces task	Adolescents showed genotype-dependent neural sensitivity (ventral striatum) to negative social cues as well as the oxytocin receptor gene-genotype rs237915 was found to moderate social and emotional problems after stressful experiences.
Weissman et al. (2019)	179	10-16	Experienced neighborhood and school crime, peer victimization, or discrimination	-	Brain function	Emotional faces task	Adolescents with greater threat exposure showed more internalizing problems as well as stronger negative coupling between the vmPFC and respiratory sinus arrhythmia, which is associated with decreased internalizing problems.

Wymbs et al. (2020)	55	7-16	Childhood adversity	-	Brain function	Emotional Go-NoGo task	Youth with CA showed increased neural reactivity (amygdala, ACC, insula, nucleus accumbens, and frontal pole) to threat stimuli and the impact of CA on threat processing was found to be moderated by maternal support.
Emotion Regulation							
Curtis & Cicchetti (2007)	87	6-12	Maltreatment	-	ERPs	-	Maltreated youth showed greater right hemisphere activity in the parietal region of the cortex, whilst non-maltreated youth showed increased activity in left hemisphere activity.
Rudolph, Skymba, et al. (2020)	43	*M* = 15.44	Peer victimization	-	Brain function	Emotion regulation task	Adolescents exposed to high levels of peer victimization demonstrated poor emotion regulation (more positive amygdala-right vlPFC connectivity) in the context of negative emotional stimuli.

Endocrine Response

Reid et al. (2021)	290	7-15	Institutional rearing	Social support (incl. friendships)	Salivary cortisol	-	Quality of social support, but not necessarily previous institutionalization experiences, predicted changes in measures of diurnal cortisol patterns across early adolescence. Specifically, higher levels of social support were associated with lower bedtime cortisol levels.

Table S4. Excluded studies examining the impact of childhood adversity on adolescent functioning across neurobiological, psychological, and social domains. Thirteen articles investigating the impact of childhood adversity on adolescent neurobiological-, psychological-, and social functioning were excluded from the review due to missing friendship support or stress measures. Studies found that adolescents with childhood adversity show greater behavioral (social) problems, blunted neural responses to rewards, maladaptive emotional processing as well as poorer emotion regulation. Abbreviations: ERPs = event related potentials; EEG = electroencephalogram; (m)PFC = (medial) prefrontal cortex; CA = childhood adversity; ACC = anterior cingulate cortex; (vl)-, (vm)PFC = (ventrolateral)-, (ventromedial) prefrontal cortex.

Paper	*N*	Age (years)	Adversity	Friendship Support	Neuro-biology	Stress	Main Findings
du Plessis et al. (2019)	50	Two timepoints: 9, 14	Peer victimization	-	Brain structure at 14 & endocrine measures	-	Youth with low daily cortisol output showed greater levels of peer victimization which was associated with smaller right vlPFC surface area at age 14.
K. H. Lee et al. (2020)	152	12-17	Peer victimization	-	Brain structure	-	Adolescent peer problems may have an indirect effect on depressive symptoms through altered (increased) nucleus accumbens volume.
Malhi et al. (2019)	202	12-18	Emotional trauma (abuse, neglect)	-	Brain structure & endocrine measures	-	Smaller left hippocampal volumes were found in adolescents with high emotional trauma carrying the NR3C1 ‘ G’ allele compared to adolescents with mild emotional trauma carrying the same genes and allelic variant.

Malhi et al. (2020)	202	12-18	Emotional trauma (abuse, neglect)	Perceived social support (incl. friends)	Brain structure	-	Adolescents with severe emotional trauma had smaller left hippocampal volumes as well as less perceived social support from friends, family, and significant others, compared to adolescents with minimal trauma exposure.
Teicher et al. (2010)	848	18-25	Childhood adversity	-	Brain structure	-	Adolescents with CA showed increased mean radial diffusivity and decreased fractional anisotropy in the corpus callosum and the corona radiata.
Vargas et al. (2019)	104	*M* = 18.02	Peer victimization	-	Brain structure	-	Adolescents who experienced peer victimization reported greater depressive symptoms and showed smaller mOFC volumes.

Table S5. Excluded studies examining the impact of childhood adversity on adolescent brain structure. Six articles investigating the impact of childhood adversity on adolescent brain structure were excluded from the review due to missing friendship support or stress measures. All studies reported altered brain structure in adolescents with childhood adversity. For example, studies investigating adolescents with severe emotional trauma found smaller left hippocampal volumes as well as less perceived social support in individuals with greater trauma exposure. Moreover, studies investigating adolescents with experienced peer victimization reported surface area reductions particularly surrounding frontal cortical volumes. Abbreviations: (vl)PFC = (ventrolateral) prefrontal cortex; CA = childhood adversity; (m)OFC = (medial) orbitofrontal cortex.

Paper	*N*	Age (years)	Adversity	Friendship Support	Neuro-biology	Stress	Main Findings
Herd et al. (2018)	167	Three timepoints: 14, 15, 16	-	Perceived secure relationship quality (incl. friendships)	Brain structure	-	Adolescent behavioral inhibitory control was found to mediate the link between perceived stress and adolescent secure relationship quality with parents, but not with peers.
Holmes et al. (2020)	91	25	-	-	Brain function	-	Adolescent (deviant) peer relationships at ages 20 and 21 were found to predict frontostriatal resting state connectivity at age 25.
Kumar et al. (2019)	55	12-14	-	-	Brain function	Peer evaluation task	During peer evaluations, adolescents encoded social values in the mPFC.
C. L. Masten et al. (2010)	20	12-13	-	-	Brain function	Cyberball	Adolescents showed greater neural activity (dmPFC, mPFC, precuneus, and pSTS) during observed social exclusion relative to inclusion, which was linked to greater prosocial behavior following exclusion.

C. L. Masten, Eisenberger, Pfeifer, & Dapretto (2013)	23	12-13	-	-	Brain function	Cyberball	Adolescents with (heightened sensitivity to) firsthand rejection experiences were more likely to showed greater neural activity in threat-related processing brain regions (incl. dACC and amygdala).
C. L. Masten, Eisenberger, Pfeifer, Colich, et al. (2013)	16	Two timepoints: 10, 13	-	-	Brain function	Cyberball	Adolescent pubertal development from age 10 to 13 was positively related to empathic concern and personal distress at age 13 as well as predicted heightened neural responses (dmPFC and temporal pole) when observing social exclusion.
McQuaid et al. (2019)	83	11-14	- *Note: maternal report of negative major life event stress was assessed during pregnancy*	-	Brain structure	-	Adolescents who experienced prenatal stress showed greater gray matter density in the bilateral posterior parietal cortex as well as displayed greater risk for psychiatric symptoms and family system dysfunction.

Rudolph, Davis, et al. (2020)	45	14-16	-	-	Brain function	Cyberball	Adolescent girls with stressful parent-child relationships reported greater depressive symptoms as well as reduced neural (dACC, subgenual ACC, and anterior insular) responses during social exclusion.
Sebastian et al. (2011)	35	14-16	-	-	Brain function	Cyberball	Compared to adults, adolescents showed attenuated neural reactivity (vlPFC) during social exclusion.
Tang et al. (2019)	166	14-28	-	-	ERPs	Cyberball	Young adolescents (10-17 years) showed greater theta power to social exclusion, compared to older adolescents (18-28 years) and the functional link between theta power to exclusion and self-reported distress was strongest in young adolescents (14-17 years).
Tousignant et al. (2018)	40	12-17	-	-	Brain function	Cyberball	Compared to adults (22-30 years), adolescents (12-17 years) showed reduced neural activation (inferior frontal gyrus) whilst observing social exclusion as well as showed less prosocial behavior towards the excluded player.

Will, Crone, et al. (2016)	43	*M* = 14.10	-	-	Brain function	Cyberball	Adolescents showed higher neural activity (dorsal striatum and lateral PFC) during social exclusion as well as when sharing monetary gains with the excluders.
Yeates et al. (2014)	143	8-13	-	Peer acceptance and friendships	Brain structure	-	Adolescent perspective taking abilities (theory of mind) significantly predicted rejection and victimization by peers, which in turn predicted an increased likelihood of poorer psychosocial outcomes (incl. friendships).
Incorrect Age							
H. J. Chen et al. (2019)	90	*M* = 48.6 *Note: sample mean age outside the adolescent range*	Natural disaster	-	Brain function	-	Traumatized adults showed decreased low-frequency fluctuation in the dACC as well as reduced dACC functional connectivity with the right hippocampus and left cerebellum, compared to controls.

Daniels et al. (2011)	70	*M* = 36.24 *Note: sample mean age outside the adolescent range*	Childhood adversity	-	Brain function	Symptom provocation paradigm	Emotion regulation abilities mediated the link between CA and posttraumatic adjustment.
Hyde et al. (2011)	103	31-54 *Note: sample mean age outside the adolescent range*	-	Perceived availability of social support (incl. friends)	Brain function	Amygdala reactivity paradigm	Individuals with below average levels of perceived social support showed a significant positive correlation between threat-related amygdala reactivity and trait anxiety.
Kungl et al. (2017)	37	1-5 *Note: sample mean age outside the adolescent range*	Foster care	-	ERPs	-	Children in foster care showed dampened brain responses (N170) when viewing stranger and caregiver faces, which was also linked to insecure attachment.

Lapp et al. (2018)	90	*M* = 32.12 *Note: sample mean age outside the adolescent range*	Childhood adversity	-	Endocrine measures	TSST	Adults with severe CA showed blunted salivary cortisol response to the TSST as well as elevated cortisol levels at pretest, as well as 20- and 40-min post-TSST.
Leicht-Deobald et al. (2018)	31	18-65 *Note: sample mean age outside the adolescent range*	Childhood adversity	-	Brain function	MIST	Individuals with CA who reported higher levels of co-worker social support showed reduced neural reactivity (amygdala) during an arithmetic stress task.
Muetzel et al. (2019)	2602	Two timepoints: 7/8, 10 *Note: sample mean age outside the adolescent range*	Peer victimization	-	Brain structure	-	Children who experienced peer victimization showed thicker cortex in the fusiform gyrus compared to those without victimization experiences.

Traumatic Brain Injury

Bigler et al. (2013)	12	8-12	-	Peer acceptance and friendships	Brain structure	-	Four of the nine youth with TBI had no mutual friends, four also received low peer acceptance ratings, and two were perceived by peers as having high levels of rejection/victimization in the classroom. *Note: Empirical studies only including participants with TBI were excluded.*
Yeates et al. (2013)	87	8-13	-	Peer acceptance and friendships	Brain structure	-	Youth with severe TBI demonstrated greater peer relationship problems (incl. higher levels of peer rejection and victimization) as well as a lower likelihood of having a mutual friend, which was related to white matter volumes in several posterior brain regions.

Missing Multiple Search Criteria

Say et al. (2014)	92	11-18	Childhood adversity	-	-	-	Adolescents with psychogenic non-epileptic seizures were more likely to report CA as well as lower levels of self-esteem.
van Harmelen et al. (2016)	771	Two timepoints: 14, 17	Childhood adversity	Friendship quality	-	-	Friendship support in 14-year-old adolescents with CA may reduce depressive symptoms at age 17.

Missing Empirical Research

Beauchamp et al. (2020)	-	-	-	-	-	-	*Note: No findings available due to protocol paper.*
Bruijel et al. (2018)	-	-	-	-	-	-	*Note: No findings available due to protocol paper.*
Cryan & Dinan (2013)	-	-	-	-	-	-	*Note: No findings available due to commentary.*

Hoffman et al. (2019)	-	-	-	-	-	-	*Note: No findings available due to protocol paper.*
McLaughlin et al. (2020)	-	-	-	-	-	-	*Note: No findings available due to review paper.*

Table S6. Excluded studies with multiple missing search criteria. Twenty-nine articles were excluded from the review due to multiple missing search criteria. Thirteen studies recruited adolescents without a recorded history of childhood adversity. The sample mean age of seven articles fell outside the predefined adolescent age range (10-24 years). Two studies only included patients with traumatic brain injury and two more studies did not collect any neurobiological stress measures. Finally, five studies were excluded due to missing empirical research (incl. protocol, commentary, or review papers). Abbreviations: (dm)PFC = dorsomedial prefrontal cortex; pSTS = posterior superior temporal sulcus; (d)ACC = (dorsal) anterior cingulate cortex; (vl)PFC = (ventrolateral) prefrontal cortex; CA = childhood adversity; ERPs = event-related potentials; TSST = trier social stress task; MIST = montreal imaging stress task; TBI = traumatic brain injury.

	Risk of Bias (Quality) Assessment
1.	Did the study address a clearly defined question?
2.	Is the sample representative of the defined population?
3.	Was the target group appropriately matched to a control group?
4.	Were well-established measure(s) used to assess friendship support?
5.	Were well-established measure(s) used to assess CA?
6.	Did the authors account for all confounding factors?
7.	Did the authors provide a justification that their sample size is appropriate beyond just citing convention in the literature?
8.	Did the authors report effect sizes or confidence intervals for the main findings?
9.	Did the authors ensure the reproducibility of their research findings?

Table S7. Summary of nine risk of bias (quality) assessment questions. For each available quality marker articles could score one point and up to nine points in total. Assessments were performed by two independent reviewers.