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Abstract

Experiences of childhood adversity are adverse experiences during childhood, such as abuse, neglect, poverty, and family dysfunction. These adverse experiences might make individuals vulnerable to mental health problems through their effect on brain development and brain functioning. Different dimensions of childhood adversity could have different effects on the brain and mental health. The exact mechanisms through which childhood adversity is related to the brain are not clear yet. The current study investigated the role of total childhood adversity, threat, and deprivation on anterior cingulate cortex-activity in response to stress in young people of age 16-26 (N=60). A cumulative approach was used to look at the role of total childhood adversity on anterior cingulate cortex-activity, a dimensional approach investigated the separate roles of the two dimensions threat and deprivation. Participants filled out a retrospective questionnaire about childhood adversity experiences (CTQ) and underwent a stressful fMRI task (MIST). Childhood adversity, threat and deprivation were expected to show a negative relationship with anterior cingulate cortex-activity in response to stress. The current study showed no evidence for a relationship between total childhood adversity and anterior cingulate cortex-activity in response to stress, nor for a relationship between the separate dimensions of threat and deprivation and anterior cingulate cortex-activity in response to stress. More research is needed to further study the underlying mechanisms by which childhood adversity is associated with brain development to help improve mental health in young people.

Keywords: childhood adversity, threat, deprivation, anterior cingulate cortex, ACC-activity, functional imaging.

Introduction and theoretical framework

Childhood adversities (CA) are adverse experiences during childhood, such as abuse, neglect, poverty, and family dysfunction. About 50 – 68 % of the population of young people experienced at least one CA (Broekhof et al., 2022; McLaughlin, 2016). Being exposed to at least one CA is associated with an increased risk of psychiatric disorders, such as mood disorders, anxiety and ADHD (Björkenstam et al., 2016; McLaughlin et al., 2012) as well as substance misuse, poor educational outcomes and chronic health conditions (Bellis et al., 2014).

Experiences of CA might make individuals vulnerable to mental health problems through their effect on brain development and brain functioning (e.g. Teicher et al., 2016). The exact mechanisms through which CA affects the brain are not quite clear yet. Identifying those mechanisms is important to be able to intervene early and support children during development. Brain development is characterized by periods of heightened plasticity, during which environmental factors may have more impact (Gabard-Durnam & McLaughlin, 2020). CA can be one of those environmental factors, that may affect neurobiological mechanisms and increase the risk of mental health problems and behavioral problems (Nelson III & Gabard-Durnam, 2020). An important neurobiological mechanism, related to stress, is the HPA-axis. The HPA-axis is responsible for the production of the stress hormone cortisol. The general cortisol response of children and young adults with experiences of CA is lower than in children without experiences of CA (Counts et al., 2022). Since the cortisol response affects receptors in the hippocampus and amygdala (Fowler et al., 2021), the stress response might be a mechanism affecting brain regions important for the processing of stress.

A possible underlying mechanism in the relationship between CA and mental health is the reactivity of the salience network (SN) (McLaughlin et al., 2019). The SN is involved in the detection and filtering of salient stimuli. By integrating sensory, emotional and cognitive information, the SN contributes to several complex brain functions such as communication and social behavior (Uddin et al., 2017). An important region within the SN is the anterior cingulate cortex (ACC). A longitudinal study looked at the SN and its response to acute stress after childhood trauma exposure. They looked at the connectivity between the SN and the default mode network (DMN) and found weakened connectivity to be a potential risk factor for the development of later perceived stress-related symptoms (Zhang et al., 2022). The ACC has been implicated in integrating input from multiple sources to facilitate and modulate affective responses, cognitive abilities, and emotion responses (Dreisbach & Fischer, 2015). Specifically, research has shown that the ACC is involved in the affective component of conflicting and unexpected situations (Braem et al., 2017).

The importance of tha ACC in mental health after CA is underlined by several neuroimaging studies, that found reduced ACC volume in individuals exposed to CA (reviewed by Bolsinger et al., 2018). For instance, a study comparing people with and without mental health problems found that war veterans with post-traumatic stress disorder (PTSD) symptoms had reduced ACC volume compared to war veterans without PTSD (Bolsinger et al., 2018). In healthy people, studies found reduced ACC volume to mediate the association between CA and emotion recognition (Rokita et al., 2020). Moreover, more experiences of CA at age 6-17 is related to more reduced ACC volume than in younger children (Baker et al., 2013). This could be explained by the protracted development of the ACC.

Apart from differences in brain morphology, functional neuroimaging studies show altered brain activity in the ACC in individuals exposed to CA. Exposure to stress stimuli and greater feelings of anxiety are related to ACC-activity; more specifically, Banihashemi et al. (2015) found a negative correlation between both physical and emotional abuse and ACC-activity. Stevens et al (2016) found a negative association for physical abuse and ACC-activity in a group of people with PTSD. A negative correlation has also been found between the severity of CA and the ACC-activity (Banihashemi et al., 2015; Stevens et al., 2016). They therefore suggest ACC-activity to be a moderator of the effect of CA on psychopathology. Furthermore, higher levels of childhood trauma were associated with reduced stress-related activity in the ACC in adults (Zhai et al., 2019). Moreover, higher activation of the ACC is related to better inhibition in children with experiences of CA (Zhai et al., 2019).

In studies mentioned before, adversities were summed independent of the nature of the adversity or based upon the severity of the CA. This is known as a cumulative approach (Evans et al., 2013). This approach builds on the evidence that more experiences of CA are associated with higher risks of mental health problems (Bellis et al., 2014; Björkenstam et al., 2016). An alternative approach is that of the dimensional model of adversity and psychopathology (DMAP). The DMAP is used in research to distinguish between the effects of different types of adversities on psychopathology and ACC-activity later in life (McLaughlin et al., 2014). One way to do so, is separating two types of dimensions of early life experiences, namely those that comprise the absence of expected cognitive and social learning experiences (i.e. deprivation experiences) from the impact of experiences reflecting harm or threat of harm to the child (i.e. threat experiences). Threat and deprivation may have unique influences on brain development (McLaughlin et al., 2014). Threat has the largest associations with brain regions involved in emotional processing (McLaughlin et al., 2014). Therefore, changes in the salience network, including the ACC, are expected in children with experiences of threat (McLaughlin et al., 2019). This expectation was confirmed by Weissman et al. (2020), who found that threat was associated with lower ACC activation when viewing fearful faces. Moreover, threatful experiences such as violence are related to lower emotion regulation, while deprivation such as poverty is not (Lambert et al., 2017). Also, when comparing experiences of stress mechanisms in threat and stress mechanisms in deprivation, more evidence is found for stress response systems mediating the association between threat and psychopathology than for the association between deprivation and psychopathology (Smith & Pollak, 2020).

In the current study both the cumulative and the dimensional approach are used. The first question addressed in this study is: Is the ACC-activity in response to stress in young adults related to the severity of CA? The expectation is that CA severity is negatively associated with ACC-activity during stress (Banihashemi et al., 2015; Stevens et al., 2016; Zhai et al., 2019). This is based on literature that indicates that higher levels of childhood trauma are negatively correlated with ACC-activity (Banihashemi et al., 2015; Stevens et al., 2016; Zhai et al.,2019). Moreover, previous literature suggests more experiences of CA to be related to more mental health problems (Bellis et al., 2014; Björkenstam et al., 2016). The second question that will be answered in the current study is testing the dimensional approach: Is the activity in the ACC in response to stress different for young people who experienced threat compared to those who experienced deprivation in early life? The expectation is to find a negative relationship for both deprivation and ACC-activity as well as for threat and ACC-activity, but that this relationship is stronger between threat and ACC-activity than between deprivation and ACC-activity (Lambert et al., 2017; McLaughlin et al., 2019; Weissman et al., 2020). This is based on studies that found negative relationships between threatful experiences and emotion regulation, but not or less for experiences of deprivation (Lambert et al., 2017); McLaughlin et al., 2019) and a stronger relationship between threat and brain regions involved in emotional processing (Mclaughlin et al., 2014).

Methods

Sample

The sample consisted of 60 participants (23 males, 37 females, 16 to 26 years old, M= 22.57 years, SD= 2.68). Inclusion criteria for the RAISE study were; age between 16-26 years, right-handed, BMI between 18.5 and 29.9 kg/m2, and self-reported experiences of adversities within the family environment before the age of 16 (e.g. emotional, sexual and/or physical abuse, emotional and/or physical neglect, parental mental health problems, marital conflict). Exclusion criteria were learning disabilities that require educational support or medication, other medication likely to compromise with immunological data, current disorders, alcohol or substance abuse, contraindications to MRI.

The current study has a cross-sectional design and uses data collected as part of the RAISE study (Moreno-López et al., 2021). The recruitment of RAISE participants was done through two ways; through re-contacting participants from the Neuroscience in Psychiatry Network community cohort study, and through distributing flyers were distributed in colleges, Addenbrooke's hospital (UK) and on social media. All data in the current paper was obtained via the RAISE study, including fMRI preprocessing steps.

Procedure

Interested participants were telephoned by a member of the RAISE team to explain the purpose of the study and to assess their eligibility. Participants underwent 3 phases. Phase 1 comprised an online assessment of CA and mental health functioning. Phase 2 comprised a laboratory assessment day to assess brain responses to stress. Phase 3 comprised an online follow-up assessment to assess mental health functioning.

The National Research Ethics Service (NRES) Committee East of England-Cambridge Central and external reviewers from the Royal Society (RGF\R1\180064 and RGF\EA\180029) have approved the final protocol, ICF, applicable recruiting materials of RAISE (IRAS, 241765). Informed consent of the participants was given both at the phone call and before the laboratory assessment day. The principal investigator of RAISE approved using the RAISE data for the current study.

Instruments

The RAISE study involved many different instruments in the three phases of the study. The current study focuses on the assessment of CA (phase 1), and stress responses (phase 2).

Childhood trauma questionnaire (CTQ)

CA was assessed with the CTQ, a standardized, retrospective self-report instrument that measures the severity of different types of childhood trauma. The questionnaire consists of 28 items, distributed on five clinical subscales: emotional abuse, physical abuse, emotional neglect, physical neglect, sexual abuse. Each item is answered on a 5-points Likert scale ranging from 'never' (1), to 'often' (5). The CTQ is found to be internally consistent on all scales in a clinical population, and in all scales except for physical neglect in a typically developing population (Hagborg et al., 2022). Test-retest reliability was substantial, with higher consistency in older adolescents (Hagborg et al., 2022). Based upon other studies (e.g. Banihashemi et al., 2021; Lambert et al., 2017), in the current study, the average of the three abuse subscales (physical abuse, emotional abuse, sexual abuse) represents the threat variable. The average of the two neglect subscales (physical neglect, emotional neglect) represents the deprivation variable (Banihashemi et al., 2021; Lambert et al., 2017). A higher score indicates greater exposure.

Montreal imaging stress task (MIST)

Stress responses in the ACC are assessed with the MIST in the MRI scanner, which consists of mental arithmetic tasks with an induced failure component (Dedovic et al., 2005). The MIST shows to be able to elicit stress reactivity and to have a strong repeatability for neural peak activity in the ACC (Goodman et al., 2020). Figure 1 shows the different conditions of the task. First, a training session was done outside the MRI scanner. Participants could practice the task for 5 minutes. During the training session, the average time needed to solve the arithmetic problems was recorded. This time was used to set a default time for the experimental condition. Next, within the MRI scanner, participants completed the MIST which consisted of 3 conditions: experimental, control and rest. During the experimental session, the average time measured during the training minus 10% is set as default time. This induces a high failure rate. When a participant answers three consecutive problems correct, another 10% will be taken of their time. Between items, the computer shows that the participant needs to have 80-90% correct answers and that they need to improve. After each item, participants see if their answer was “correct”, “incorrect” or “time out”. The control session is similar to the experimental session, except that it has no time limit. Therefore, average performance increases to about 90%. During the rest session, varying between 1 to 3 minutes, participants look at a blank screen (no tasks will be shown) and do not have to do anything.

Figure 1

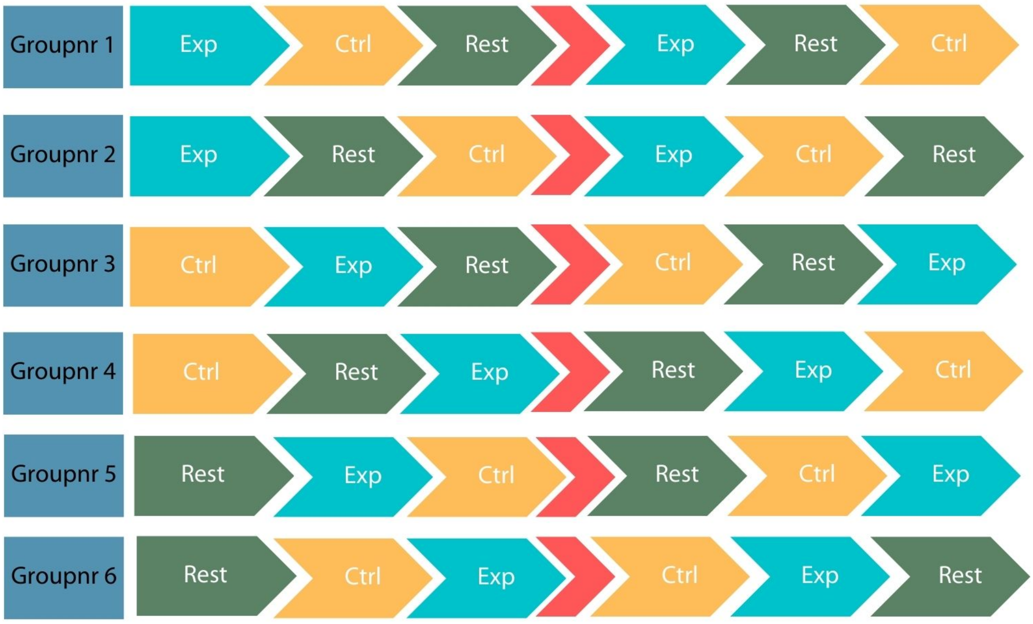
The differences between the MIST conditions: Training, Experiment, Control and Rest

Note. First, an out of the scanner training will give the participant the opportunity to practice the arithmetic problems. For all conditions, 5 difficulty levels of the arithmetic problems will be presented in random order and feedback will be presented on the screen (correct, incorrect, timeout). During training, an average time is set as default time for the experimental condition. In the scanner, participants will go through the different conditions in different orders (Figure 2). One of the conditions is the experimental condition, where most stress is induced. A time limit is set (their default time), and a performance bar is shown, showing they perform worse than 80-90%. In the control condition there is no time limit, so less stress is induced. During the rest condition, participants look at the screen and take a break.

The experimental, control and rest conditions are done twice for each participant, in different orders (Figure 2). A participant is randomly placed into a group and will have the sequence of conditions as shown in Figure 2. After a run (consisting of three conditions), verbal feedback is given to the participant, including sentences as “Please remember that your performance needs to be close to the average to allow us to use your data”.

Figure 2

The Sequences of Conditions in the MIST



Note. Participants are randomly attributed to a group, that decides the sequence in which they will go through the different conditions. Each run consists of three conditions. After a run, participants will see a screen with information about their performance (the red part). They will read for example "Please remember that your performance needs to be close to the average to allow us to use your data".

In previous studies, the MIST has induced activity in the ACC (e.g. Shao et al., 2018). The contrast used in this study was the experiment-control contrast; the standard arithmetic task in the control condition was subtracted from the experimental condition. By doing this, cognitive aspects unrelated to stress are left out.

fMRI processing

For the imaging data, a Siemens Magneton prisma-Fit MRI 3 Tesla scanner was used, equipped with a 32-channel headcoil. The statistical analyses of the fMRI data were performed according to the defaults of SPM (Ashburner & Friston, 2005). The preprocessing consists of correction of movement artifacts, detecting scanner artifacts, distortion correction, slice time correction, spatial smoothing, spatial realignment, spatial normalization and smoothing. Subjects might be excluded if the movement artifacts are extreme.

After the preprocessing, in the first-level analyses we used a general linear model (GLM) to model each participant's individual brain activity to the design (experimental versus control). In the second-level analysis we tested for group effects in our primary region of interest (ROI); the ACC, defined using the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002). Within this

ROI, a bilateral global maximum (the peak voxel across both hemispheres) was detected. Next, the cluster which the peak voxels are part of, surpassing the family-wise error (FWE) threshold of p<.05, was extracted for each participant's contrast map. These values were then averaged to get one measure of the ACC-activity during the experimental condition compared to the control condition for each participant.

Data analysis

Data were analyzed using SPSS 28 and checked with R. The significance level used in all analysis was $p < .05$. To account for multiple comparison; needed for composing models for *total CA, threat* and *deprivation,* Bonferroni was used to lower the p-value. The used alpha threshold of significance in the regressions was therefore 0.05/3= 0.0167. Exploratory analyses were done for associations between age, gender and ACC-activity. Studies found structural differences between men and women after childhood adversity in several brain regions (Everaerd et al., 2016). Then, univariate data-inspection was done to detect missing variables and outliers. Within the univariate data-inspection, descriptive statistics using dispersion measures were described. After, assumptions for linear regressions were checked. First, it is important that the relationship between the predicting variable(s) and the outcome variable is linear. This assumption was checked within the bivariate data-inspection, using Pearson's correlations and bivariate scatterplots. Second, the residuals should be normally distributed, which was checked within the regression analysis. Moreover, the residuals should be equally spread around y = 0, implying homoscedasticity. For multiple regression the assumption of multicollinearity was checked using a collinearity-analysis' VIF-values. Cook's Distance showed values have big influence the analysis. Moreover, exploratory analyses were done to explore the role of age and gender on the dependent variable ACC-activity.

A linear regression was used to answer the main question: *Is the ACC-activity in response to stress in young adults related to the number of CA?* The predictor variable is the number of CA (total CA) and consists of the sum score of the total CTQ. The outcome variable is the ACC-activity in the experimental versus the control condition. To be able to control for age and gender, a hierarchical regression will be executed. First, age and gender were the predictors of model 1. Second, the total CA variable were added into the regression in model 2.

The second question: I*s the ACC-activity in response to stress in young adults related to early life experiences of threat and deprivation?* was answered through a multiple regression. The scores on each subscale range from 5 to 25, where 5 indicates no maltreatment. In the linear regression, *threat* and *deprivation* will be the predicting variables. The outcome variable is the *ACC-activity* in response to stress as assessed in the experimental (vs control) condition in the MIST. To be able to control for age and gender, a hierarchical regression was executed. First, age and gender will be the predictors of model 1. Second, the threat and deprivation variables were added into the regression in model 2.

Results

fMRI results

Two significant clusters were found in the ROI (ACC), as described in Table 1. The cluster that contained the bilateral global maximum was a cluster containing 45 voxels (uncorrected p = 0.003). The location of the cluster is in the right ventral anterior cingulate (Figure 3). The other significant cluster is located in the right dorsal ACC. This cluster was not used for further analyses.

Table 1

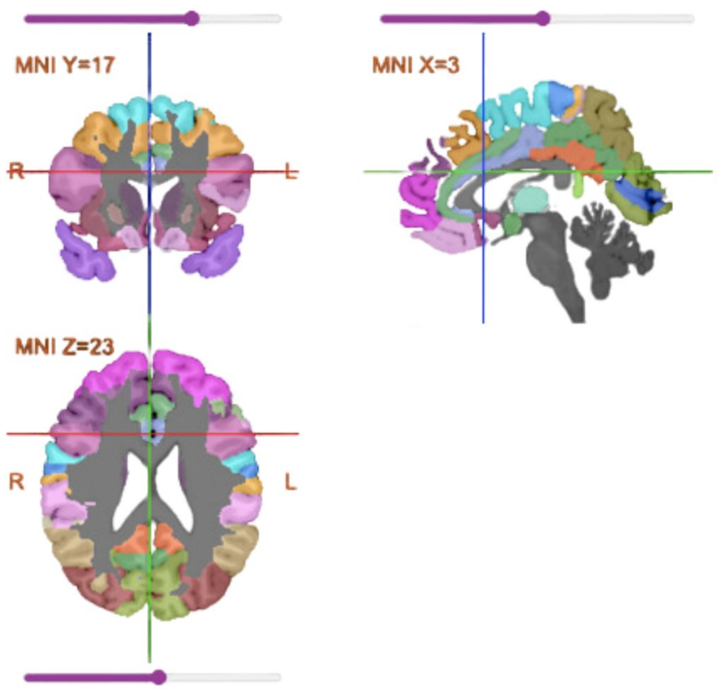
fMRI Statistics of the Two Significant Clusters in the ROI (ACC)

Cluster- level				Coordinates in mm		
*p*FWE_corr	*q*FDR_corr	*k*	*p*uncorrected			
0.003	**1.000**	**45**	**0.853**	**3**	**17**	**23**
0.026	1.000	5	0.506	0	47	5

Note. Statistics in bold are the ones corresponding to the cluster containing the peak voxel and the cluster used in subsequent analyses.

Figure 3

The Coordinates of the Global Maximum (Experiment-Control Contrast) across both Hemispheres Located in the Right Ventral Anterior Cingulate Cortex



Note. The tool used for this figure is the MNI <-> Talairach Tool. The colors correspond to Brodmann areas (based on Lacadie et al., 2008).

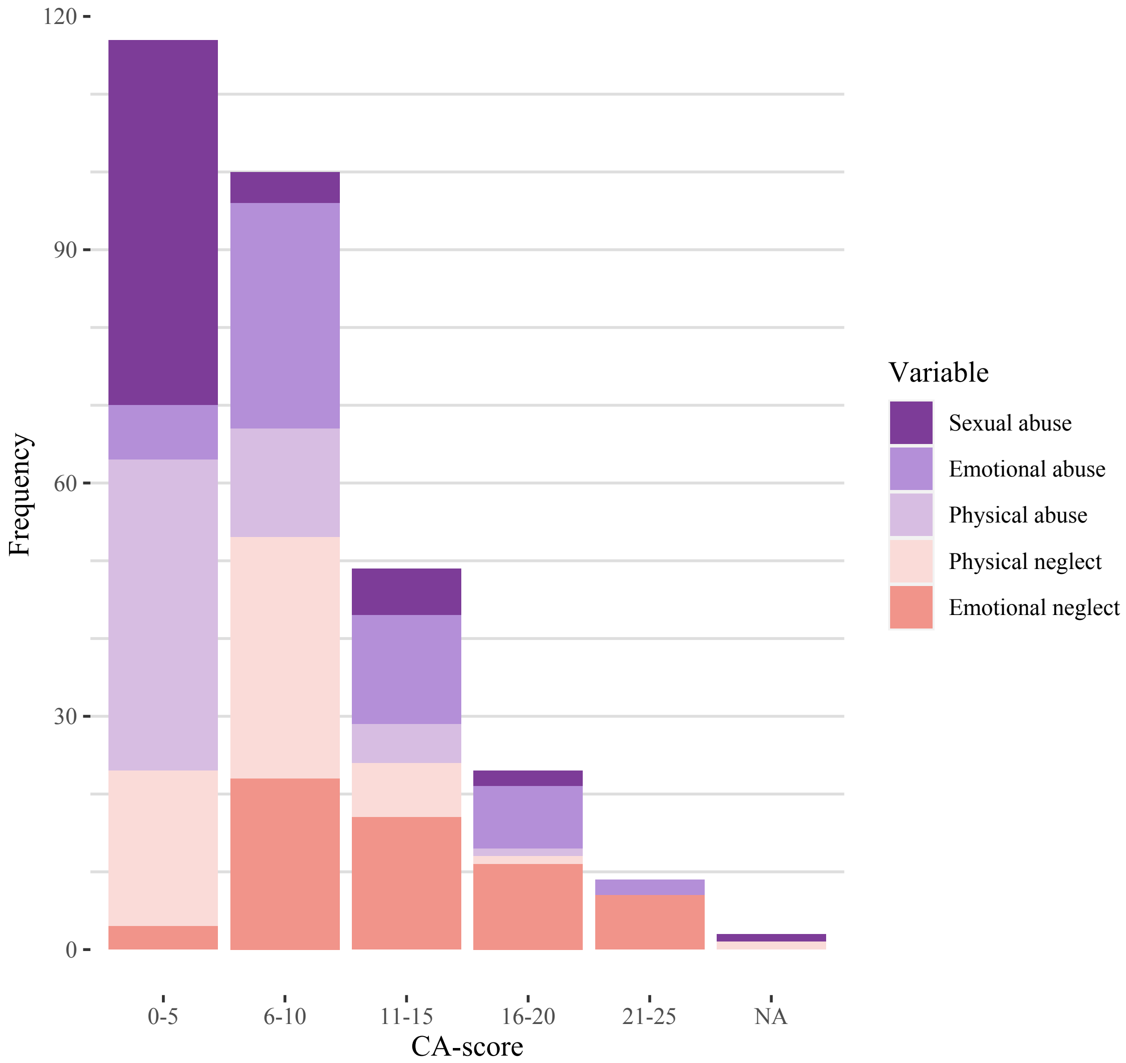
Univariate data exploration

For *total CA* there were two missing scores, for two different participants. One of the missing scores was on the sexual abuse subscale of the CTQ, resulting in one missing score for the *threat* variable. The second one was missing on the physical neglect subscale of the CTQ, resulting in one missing score for the *deprivation* variable. Because there were only two missing variables and there was no pattern, the missing values were deleted pairwise. Therefore, there may be different numbers of participants for different analyses. Since imputation of the missing variables would influence the variance and the standard error, pairwise deletion is assumed to be the best option. For *age*, *gender* and *ACC-activity* there were no missing values.

Figure 4 shows the frequency of each CTQ-subscale, showing that Emotional Neglect and Emotional Abuse are most prevalent in the sample, and Sexual Abuse is the least prevalent form of CA in the sample. Figure 4 shows that the severity of CA in this sample is low. Descriptives for the numerical variables *age, ACC-activity, total CA, threat* and *deprivation* are listed in Table 2. The assumption of normality for the dependent variable *ACC-activity* was met (Appendix A, Figure A1). Based upon the histograms and QQ-plots, the distribution of the residuals of *age* and *deprivation* can be considered normal as well. The standardized kurtosis of all variables fall within the range of acceptable values of -3 to 3 (Table 2). However, the standardized skewness does not fall within the range of -3 to 3 for all variables. Both *threat* (z = 4.02) and *total CA* (z = 3.47) are skewed to the right; most participants experienced low severity of threat and total CA. Deprivation was slightly skewed to the right as well, but with a z-score of 2.47 within the range of -3 to 3. If the multivariate normality can be assumed after doing the regressions, no problems with skewness are expected and the assumptions of regression are met.

Figure 4

Distribution of CA presented in CTQ-subscales



Note. The x-axis describes the score on the CTQ-subscale as described in the legend. 0-5 indicates participants having no experiences on that subscale. 25 is the maximum score on a subscale. The purple subscales together represent *threat,* the pink subscales together represent *deprivation*.

Table 2

Descriptives of the Numerical Variables

		Age	ACC	Total CA	Threat	Deprivation
N	Valid	60	60	58	59	59
	Missing	0	0	2	1	1
Mean		22.57	0.76	42.84	7.71	10.10
Std. Deviation		2.68	1.42	13.57	2.56	3.79
Minimum		16	-2.60	25.00	5.00	5.00
Maximum		26	3.79	80.00	15.00	19.00
z-score Skewness		-2.07	0.16	3.47	4.02	2.47
z-score Kurtosis		-0.36	-0.39	1.43	1.62	-0.39

Based upon the boxplots, that shows how the data is spread about the median, and the 1.5-Inter Quartile Range (IQR) Rule, there are no outliers for *ACC-activity* and for *deprivation* (Appendix A, Figure A2). For *threat,* there were 3 outliers that scored above the 1.5-IQR. For the *Total CA* there were 3 outliers, that scored more than 1.5-IQR higher than the mean. For *age,* there were 7 outliers that had an age of at least 1.5-IQR below the mean. This means that the younger part of our sample is less well represented. All outlier scores are real scores and not the results of errors and will therefore be used in the analyses. The outliers are expected values within the study and are the result of the inclusion criteria, and their results are therefore important for the analyses. However, it needs to be taken into account that not all parts of the population of people with experiences of CA are well-represented in the sample.

Bivariate data exploration

An important assumption for linear regression is a linear relationship between the predictor and the outcome variable. Based on the scatterplots (Appendix A, Figure A2), the relation between the predictive variables (*total CA*, *threat, deprivation)* and the response variable (*ACC-activity*) can be assumed to be linear. Moreover, the spread of the variance of the error is approximately equal for all levels of the predictive variables. The assumption of homoscedasticity can therefore be accepted.

For the multiple regression of the second question, the multicollinearity between the two predictive variables was investigated. A Pearson correlation of .657 ($p < .001$) shows a significant association between threat and deprivation. Therefore, there is potentially bivariate multicollinearity. A multicollinearity test within the regression analysis will show whether or not the multicollinearity is acceptable.

Conclusions data exploration

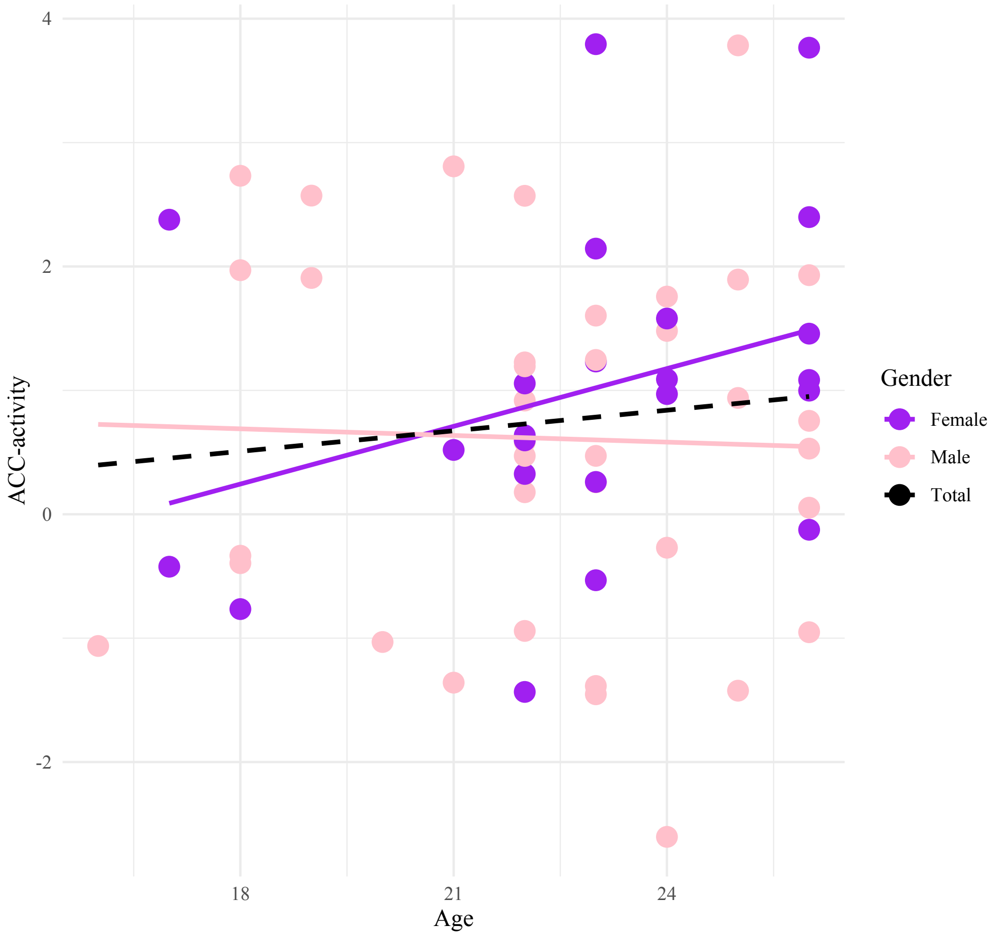
Based on the data exploration, no problems are expected with the validity of the main analysis. The distribution of the observations is normal for the outcome variable. The distribution of the residuals in the regression analysis will provide more information about the assumption of normality. Moreover, outliers are all scores within the range of our sample. However, the role of outliers must be considered because they can still influence the analyses. Therefore, analysis will be repeated without the outliers, to check the actual impact of the outliers on the analysis. Data exploration showed linear relationships between variables and the assumption of homoscedasticity is met. The distribution of the residuals will provide more information about the assumptions of the linear regressions analysis.

Age and gender as potential confounders

First, a visualization of the exploratory analyses showed a possible interaction effect of *age* and *gender* on *ACC-activity* (Figure 5). Therefore, the interaction term *age*gender* is included in the multiple regression analyses for both question 1 and question 2 as an extra control variable, beside the separate control variables *age* and *gender*. The possible interaction between *age* and *gender* in the current study means older females have higher ACC-activity than older males, while younger females have lower ACC-activity than younger males. This interaction is possibly affected by outliers of age; as mentioned in the univariate data-inspection, *age* had outliers among the younger range of participants. However, since outliers will be part of all analyses, the interaction term of *age*gender* will also be added to the analyses to investigate if it is a significant predictor of *ACC-activity,* and therefore a possible confounder.

Figure 5

Effects of Age and Gender on ACC-activity showing a Possible Interaction-effect



Note. Results of the main analyses will show whether this interaction is significant and whether this interaction term is a confounder.

Results of the main analyses

Both hierarchical regressions were performed with the first model including *age, gender,* and *age*gender* as predictors of *ACC-activity* (Table 3). Model 1 did not fit the data well (adjusted R^2 = -0.4%). Model 1 was a non-significant predictor (F (3.54) = 0.921; p= .437). The control variables *age* and *gender* did not predict *ACC-activity,* nor did the interaction term *age*gender.* The following paragraphs describe if *total CA* (question 1) or *threat* and *deprivation* (question 2) are predictors of ACC-activity, when controlling for *age, gender* and *age*gender.*

Table 3

*Coefficients of the first level of the Hierarchical Regression Model with Age, Gender and Age*Gender as Control Variables*

Model		B	SE	Beta	t	p	Part
1	(Constant)	-6.139	5.544		-1.107	.273	
	Age	0.326	0.241	0.621	1.349	.183	.179
	Gender	3.558	3.275	1.220	1.086	.282	.144
	Age*Gender	-0.171	0.143	-1.400	-1.195	.237	-.159

Question 1: *Is the ACC-activity in response to stress in young adults related to the number of CA?*

A multiple regression was done to predict ACC-activity based on the total CA score, including age and gender as control factors. The residuals are equally distributed around y=0 (Appendix A, Figure A4). There is no reason to assume that linearity does not hold in the population (Appendix A, Figure A3). Furthermore, it seems that for every predicted value the vertical dispersion is equal; the variance of the error term is the same for all values. The assumption of homoscedasticity is therefore met. Moreover, normality of the residuals can be assumed based upon the histogram (Appendix A, Figure A5). Values with high influence on the analysis are checked using Cook's Distance. Values are considered outliers when higher than 4/N. Four multivariate outliers were found. Analyses were run twice; with and without outliers. However, leaving the outliers out resulted in similar results, so only analysis with outliers included were reported.

Table 4 shows an overview of the coefficients of the regression. The first model included *age, gender* and *age*gender*, as described above. In the second model, when adding the *total CA,* still no variance of *ACC-activity* was predicted (adjusted R^2 = -0.9%). Model 2 did not fit the data well (F (4.53) = 0.873; p= .486). The addition of the *total CA* to the model did not account for significant changes in the model (F change (1.53) = 0.742; p= .393). *Total CA* had a part correlation of -11,5% and was a non-significant predictor of *ACC-activity*
(β = -0.012; t (57) = -0.862; p = .393). The negative part correlation indicates a negative relationship between *Total CA* and *ACC-activity.*

Table 4

Coefficients of the Second Level of the Regression Model with Total CA as Predictor and ACC-activity as Outcome Variable

Model		*B*	*SE*	Beta	*t*	*p*	Part
2a	(Constant)	-4.838	5.759		-0.840	.405	
	Age	0.291	0.245	0.554	1.185	.241	.158
	Gender	3.025	3.340	1.037	0.906	.369	.120
	Age*Gender	-0.147	0.146	-1.203	-1.006	.319	-.134
	Total CA	-0.012	0.014	-0.117	-0.862	.393	-.115

Question 2: *Is the ACC-activity in response to stress in young adults related to early life experiences of threat and deprivation?*

The residuals are equally distributed around y=0 (Appendix A, Figure A6). The assumption of linearity is met. Furthermore, it seems that for every predicted value the vertical dispersion is equal; the variance of the error term is the same for all values. Therefore, the assumption of homoscedasticity is met as well. Based upon the histogram, normality of the residuals can be assumed (Appendix A, Figure A7). To check multicollinearity between *threat* and *deprivation*, VIF-values were calculated, where VIF ≥ 2.5 indicates considerable collinearity. The VIF-values of *threat* (2.033) and *deprivation* (1.855) show there is no multicollinearity between the predictors. Values having high influence on the analysis are measured using Cook's Distance. Values are considered outliers when higher than 4/N. Two multivariate outliers were found. When doing the analysis without those two outliers, the adjusted R^2 of model 2 was 3%. No major differences in other statistics were found, so analyses were run with outliers included.

Table 5 shows an overview of the coefficients of the regression. The first model included the control variables and was described above. In the second model, when adding *threat* and *deprivation,* with an adjusted R^2 of -2,4%, none of ACC-activity was predicted (F (5.52) = 0.737; p= .599). The addition of *threat* and *deprivation* to the model did not account for significant changes in the model (F change (2.52) = 0.487; p= .617). When looking at the part correlations, threat predicts 1.4% of the ACC-activity and is a non-significant predictor of *ACC-activity* (β = -0.021; t (57) = -0.108; p = .915). *Deprivation* predicts -10.7% of the *ACC-activity* and is a non-significant predictor of ACC-activity (β = -0.145; t (57) = -0.796; p = .430). The negative part correlation suggests an inverse relationship between *deprivation* and *ACC-activity.*

Table 5

Coefficients of the Second Level of the Regression Model with Threat and Deprivation as Predictors and ACC-activity as Outcome Variable

Model		*B*	*SE*	Beta	*t*	*p*	Part
2b	(Constant)	-5.613	6.010		-.934	.355	
	Age	.325	.257	.620	1.266	.211	.170
	Gender	3.476	3.487	1.192	.997	.323	.134
	Age*Gender	-.169	.154	-1.377	-1.097	.278	-.147
	Threat	.012	.108	.021	.108	.915	.014
	Deprivation	-.057	.071	-.145	-.796	.430	-.107

Discussion

Conclusion

The goal of this study was to get insight into associations between CA and ACC-activity in response to stress. CA was operationalized in two different ways. First, the cumulative approach was applied where all adverse experiences were summed. Second, the dimensional approach was applied where CA was split into threat and deprivation dimensions. No evidence was found for an association between total CA and ACC-activity, nor for different dimensions of CA (i.e., threat and deprivation) and ACC-activity. These findings do not align with the hypotheses. The next paragraphs will describe potential explanations for these unexpected findings. Thereafter, strengths and limitations of the study and implications for future research will be discussed.

The first question addressed in this study was: Is the ACC-activity in response to stress in young adults related to the total severity of CA? The expectation was that CA severity is negatively associated with ACC-activity during stress (Banihashemi et al., 2015; Stevens et al., 2016; Zhai et al., 2019). In the current study, however, there was no significant association between ACC and total CA. A theoretical explanation for this unexpected finding is in the way of measuring CA in research. The study by Zhai et al. (2019) does find a significant negative relationship between ACC-activity and CA. However, they measure CA in a different way; they split CA in higher trauma and lower trauma groups. A review study found 32 ways of measuring CA (Oh et al., 2018), which can include sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect as well as household dysfunction and other adversities such as discrimination. These different ways of measuring CA account for different results on the effects of CA on (brain) development (Oh et al., 2018). Moreover, the age of the adversity plays a role in the effects on brain development (Nelson et al., 2020). Adverse experiences during critical periods of development are more likely to have long lasting effects (Nelson et al., 2020). Moreover, the sample of the study by Zhai et al. (2019) consisted of younger people (14-17 years) than the current sample with older people and a wider age range (16-23 years). This difference may affect the outcomes because both brain structure and function are still developing. During puberty especially, the ACC is maturing a lot, resulting in more self-regulating skills in young adults (Lichenstein et al., 2016). During puberty, the connections between the ACC and other parts of the SN get stronger (Lichenstein et al., 2016; Solé-Padullés et al., 2016). Therefore, a younger group of people are more likely to show less activity and connectivity in the ACC than a group of people where the ACC and their connections are more likely further developed. Underdeveloped ACC might therefore play a role in the findings of Zhai et al., (2019).

The second question in this study was: Is the ACC-activity in response to stress in young adults related to early life experiences of threat and deprivation? The expectation was to find a negative relationship for both deprivation and ACC-activity as well as for threat and ACC-activity, but that this relationship is stronger between threat and ACC-activity than between deprivation and ACC-activity (Lambert et al., 2017; McLaughlin et al., 2019). In the current study, neither threat nor deprivation was a significant predictor of the ACC-activity. Previous studies have shown evidence for distinct effects of threat and deprivation on brain development and mental health (Lambert et al., 2017; McLaughlin et al., 2014). However, splitting CA into threat and deprivation has some conceptual problems too. A first conceptual problem of splitting up CA into threat and deprivation is that adverse experiences tend to co-occur (Smith & Pollak, 2020). It is therefore hard to split them up and to see separate effects as effects of the specific type of experience. Moreover, the subtypes of adverse experiences do not have strict boarders; it is hard to define when a certain adversity is threat or deprivation.

Importantly, one of the possible explanations for the unexpected findings in both the cumulative and dimensional approach is that there might not be an association between CA and ACC-activity in response to stress. The ACC might be more involved in later psychopathology and mental health problems, which were not part of the current sample (Solé-Padullés et al., 2016). The total SN might be more important for the effects of CA than the ACC alone (Shanmugan et al., 2020).

Strengths and limitations

The current study complements previous research in several ways. By including both the cumulative and the dimensional approach to measuring childhood adversity in the same study, differences between both approaches could be observed. The different approaches accounted for exploring different effects of CA. Furthermore, a combination of neuroimaging data and a questionnaire provided information about the experience of childhood adversity and the brain. Moreover, the MIST task used to elicit stress in the fMRI is shown to be a reliable and consistent measure of stress, showing peak activation in the ACC repeatedly (Goodman et al., 2020).

However, the current study also has some limitations. First, the relatively small sample size could give an unreliable estimate of the associations in the population. This relatively small sample size was due to the onset of the COVID-19 pandemic during data collection. The chance for a Type-II mistake would have been smaller with a bigger sample (or less predictors). In the current study, no effects were found, while these effects might be there in the population (=Type-II mistake). Furthermore, there was no random sampling, which could account for a less representative sample of the population. However, both genders were equally represented.

Another limitation of this study was that CA was only measured through a retrospective questionnaire. Previous studies found differences between objective and subjective measures of childhood adversities (e.g. Zimmerman & Farrell, 2013). Because the CTQ consists of the participants view only, an extra objective and prospective measure of childcare services, teachers, or parents would make a more reliable CA measure. Moreover, the CTQ included measures for the prevalence of adverse events. However, it did not include measures of the subjective way the event was experienced. In the current study, severity was measured through the prevalence of events (never to often), where more adverse events represent higher severity. However, participants could experience events differently; for some young people one adverse experience would be just as severe as three adverse experiences for another young person. Moreover, recall biases should be taken into account. Participants might not be able to recall all of their adversities, reducing the severity and prevalence of certain adversities in the sample.

Next, some limitations of the fMRI processing should be mentioned. First, a limitation of the fMRI processing is that there was no access to whole brain data. Therefore, it remains unclear if there were effects of CA outside the ACC-mask. However, the focus of the current study was the ACC and the sample size (N=60) is not sufficient for reliable whole brain analyses (Marek et al., 2022). Another point of discussion is the analyses using a cluster containing the global maximum. This was done because the ACC is labeled as a single anatomical region, however, functionally there might be differences within the ACC. When analyzing the cluster around the peak voxel, you are looking at the most important subregion. Tong et al. (2016) found highly activated voxels such as the peak voxel within an ROI to be more reliable in detecting differences between groups. However, it is recommended to have a strong a priori hypothesis about the sphere (peak cluster) based upon previous research (Tong et al., 2016). Moreover, there is large intra- and inter-personal variation in the locations and shapes of functional brain regions (Llera et al., 2019).

A statistical limitation of the current study, and of most studies on childhood adversities, is that children with childhood adversities are usually outliers in the general population; severe CA is less prevalent than mild or no CA. Statistically they are outliers, but theoretically they are exactly what the study wants to measure. It is therefore not possible to remove outliers or values with high influence (measured by Cook's Distance), because it would take away association potential. The fact that outliers were found, means that these characteristics are underrepresented in the sample. Previous studies found a higher CTQ score to be related to more severe psychopathology (Newbury et al., 2018). In the current study, participants were excluded when having current psychopathology. This might account for the sample with less severe CA than other studies, which might account for some of the non-findings of the current study.

Implications and future directions

Several different biobehavioral models on the effects of childhood adversity have been studied over the past years (Dunn et al., 2018; McLaughlin et al., 2019). The current dominant view is that the examination of specific effects of different types of stress or adversity, such as threat and deprivation, provides information about specific mechanisms (e.g. Lambert et al., 2017; McLaughlin et al., 2014). However, the aforementioned conceptual problems of this way of splitting adversity provide more reason for a reconceptualization of CA. Many different factors could affect the way a person deals with adversities as well as their effects on brain and behavior. Smith and Pollok (2021) propose a more topological approach, where various factors or features influence the way an event is experienced. In their topological approach, they propose four different kinds of features that affect how a person experiences adversity; features of the event, features of the environment, features of the social context, other individual difference factors. Childhood adversity and their consequences are a complex field of study. Different types of adversities might affect different parts of the brain (Schäfer et al., 2023). However, it does not only affect the brain, but chronic stress also affects endocrine and immune systems (Bucci et al., 2016). Furthermore, biological predispositions and epigenetic modifications also affect the way childhood adversity is experienced (Bucci et al., 2016; Zhu et al., 2022). These factors, as well as environmental factors such as social support, could be seen as risk and resilience factors; factors that affect mental health after adversity (Fritz et al., 2018).

Futures studies should further investigate the dimensional models and take into account the topological approach and individual features as proposed by Smith and Pollok (2021) as well. By including different features of the event, environment, social context and individual factors, the true effects of childhood adversity on the ACC could be explored. Additionally, it is important to use a longitudinal design to be able to know the directions of the associations; are these features resilience factors or are they the consequence of adversity? With a longitudinal design, a study would know what the brain activity is before and after an adversity and see how activity changes over time. To explore this, neuroimaging should be matched to observed behavior to understand the underlying mechanisms. Beside using these different features of childhood adversity, future studies could focus not only on activity, but also on the connectivity of the ACC with other brain regions. Several studies focused on connectivity in the connection between the amygdala and the ACC following adversity, but so far with conflicting results (as reviewed by Holz et al., 2023). Research using the different features and factors, in a longitudinal study, looking at ACC-amygdala connectivity, should provide more information on the possible mechanisms of childhood adversity on the brain.

Apart from the scientific implications, the current study also has societal implications. About 50 – 68 % of the population of young people experienced at least one CA (Broekhof et al., 2022; McLaughlin, 2016), increasing the risk for mental health problems (Björkenstam et al., 2016). Studying the underlying mechanisms of CA and their effects could help reduce these mental health problems in young people. It could help professionals develop effective interventions and tools. Moreover, studying different dimensions of CA may have implications for different interventions for experiences of threat and experiences of deprivation (Schäfer et al., 2023).

In conclusion, the current study found no relationship between CA and ACC-activity in response to stress for both the cumulative and the dimensional approach. Further research on the mechanisms of CA and its relationship with brain development is needed to have a better understanding of CA and to improve young people's mental health.

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Appendix A

Figure A1

Normal Distribution of the Dependent Variable ACC-activity

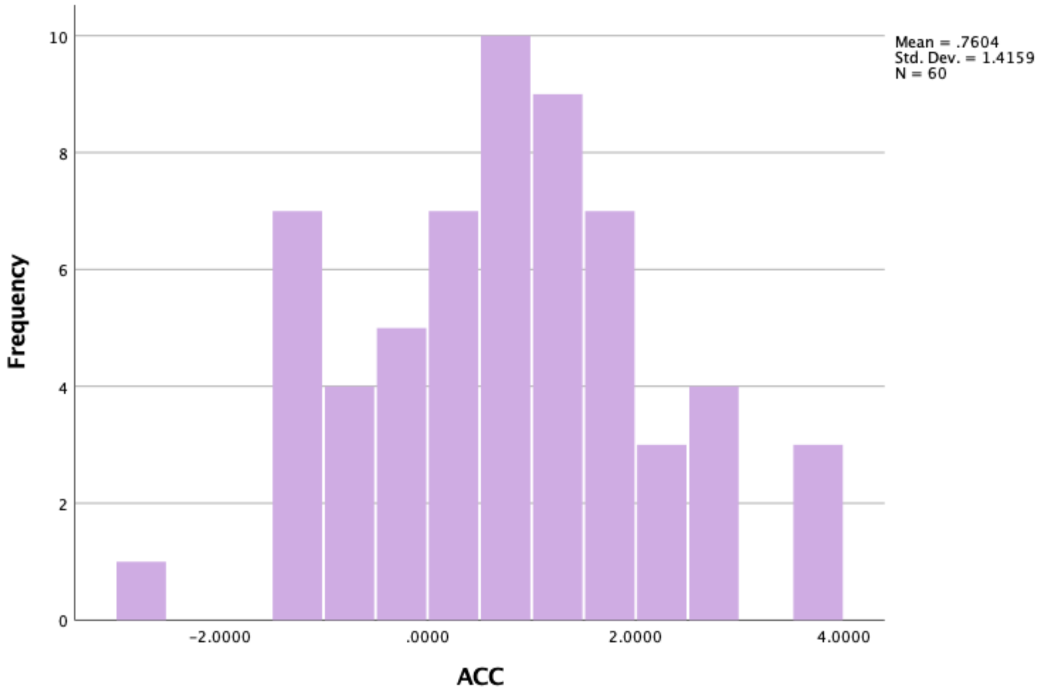


Figure A2

Boxplots of the Numeric Variables showing Outliers for Age, Total CA, and Threat

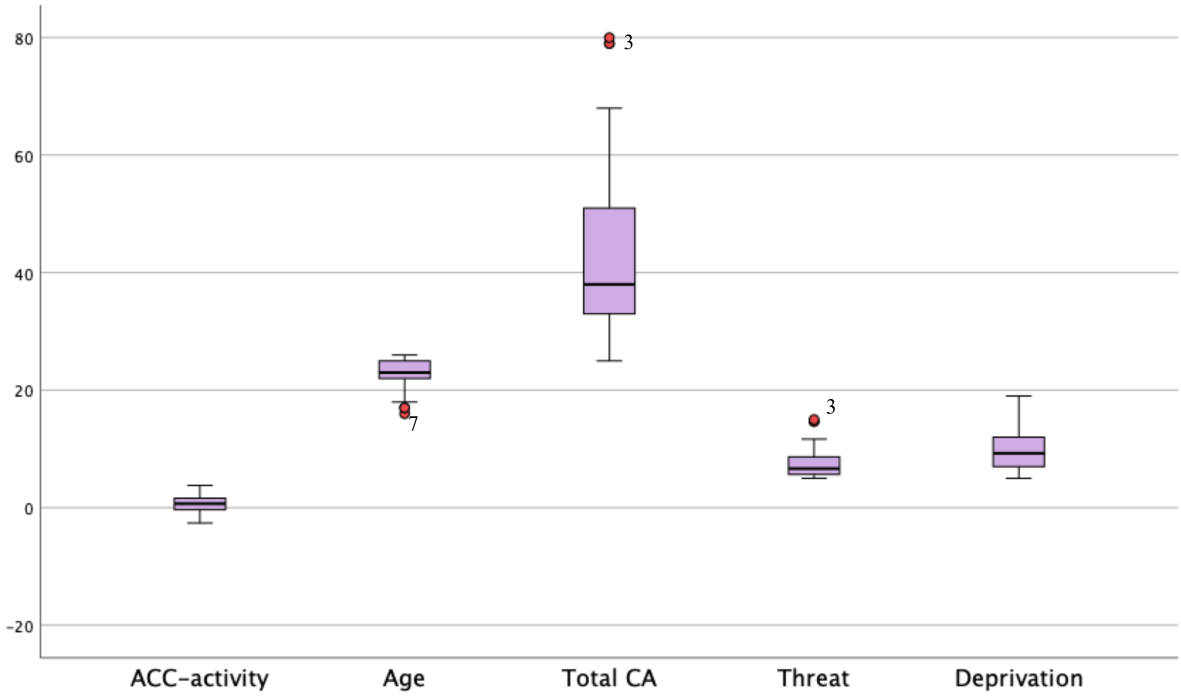
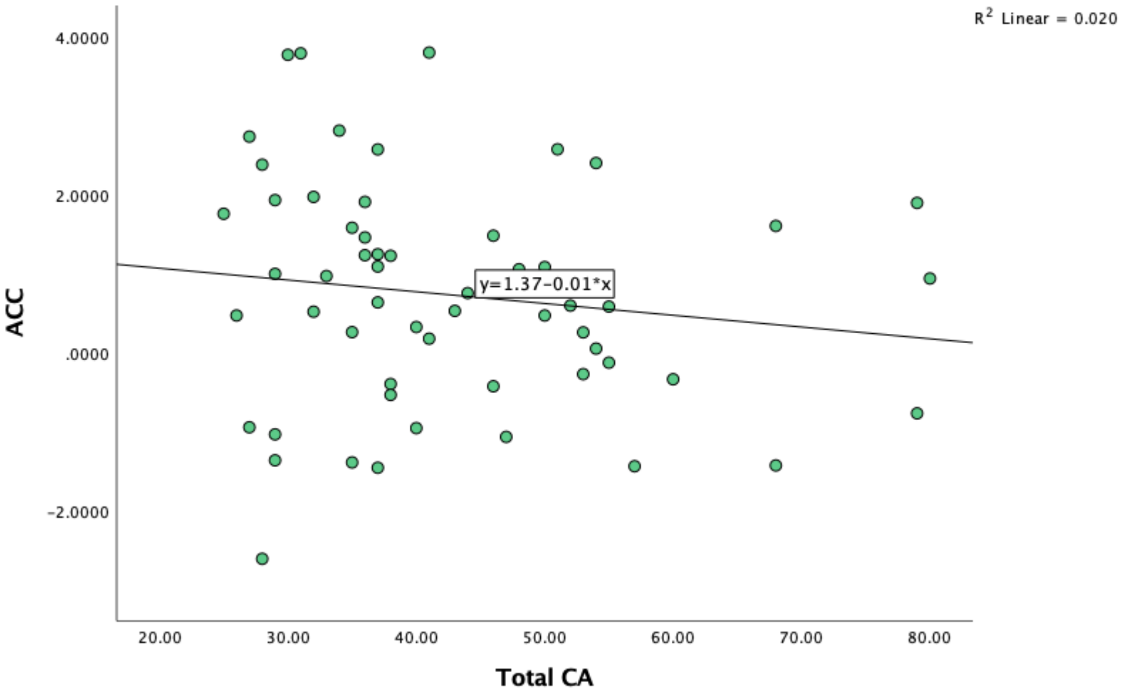


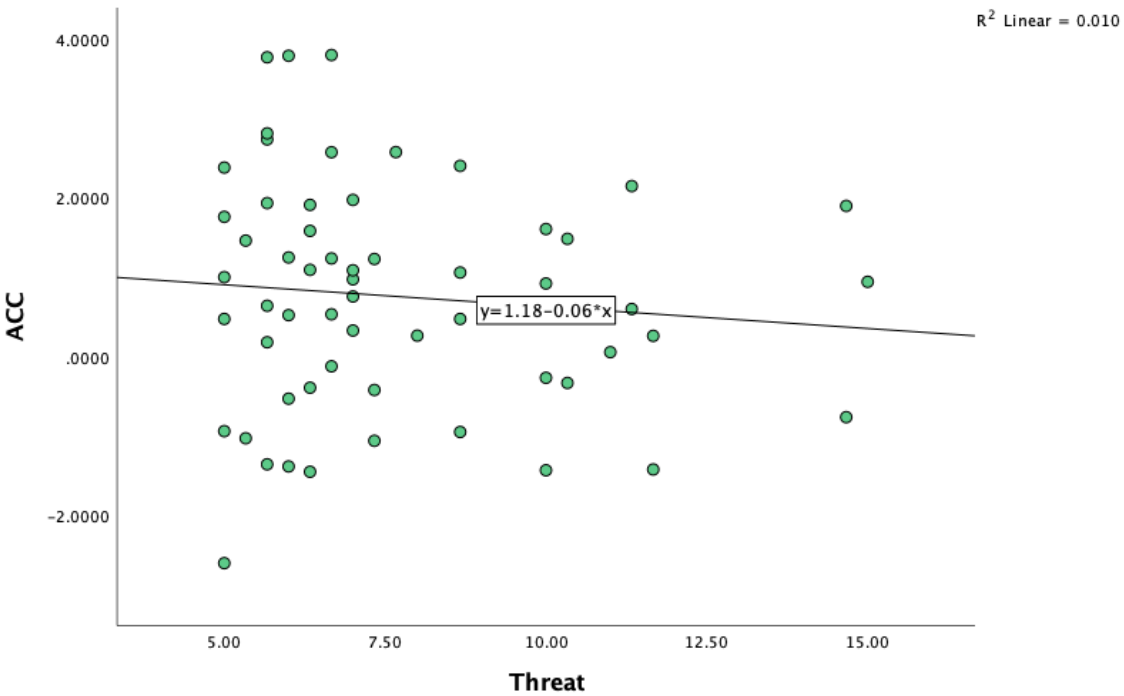
Figure A3

Scatterplots of the Linear Relationship between the Dependent Variable ACC-activity and the Independent Variables Total CA (A), Threat (B), Deprivation (C)

A.



B.



C.

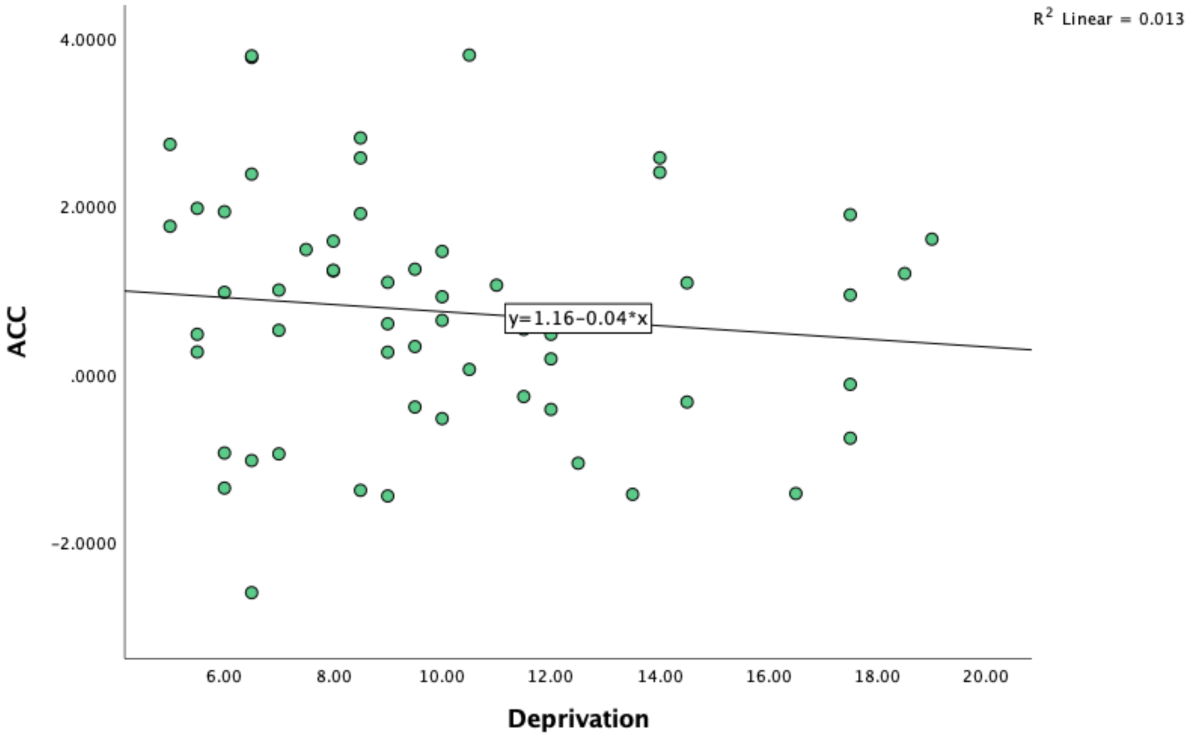


Figure A4

*Scatterplot of the Residuals of Question 1, including the Dependent Variable ACC-activity and the Independent Variables Total CA, as well as the Control Variables Age, Gender and Age*Gender*

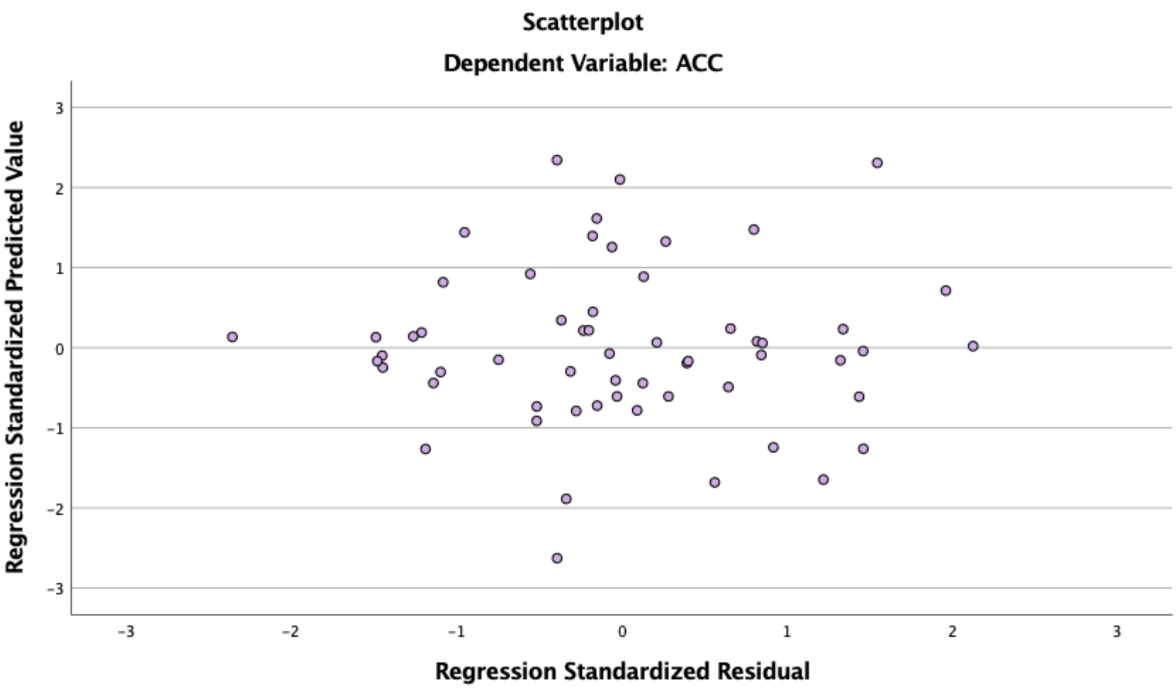


Figure A5

Distribution of the resiudals of Question 1, with Total CA as a predictor of ACC-activity and Age and Gender as Control Variables

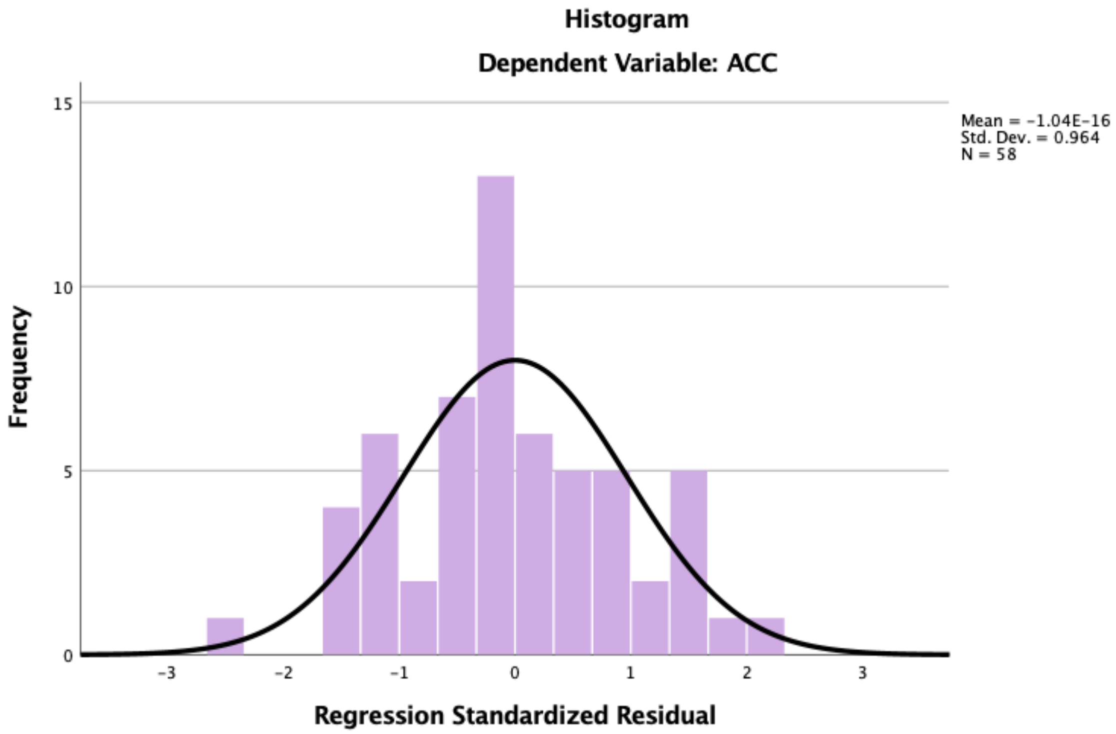


Figure A6

*Scatterplot of the Residuals of Question 2, including the Dependent Variable ACC-activity and the Independent Variables Threat and Deprivation as well as the Control Variables Age, Gender and Age*Gender*

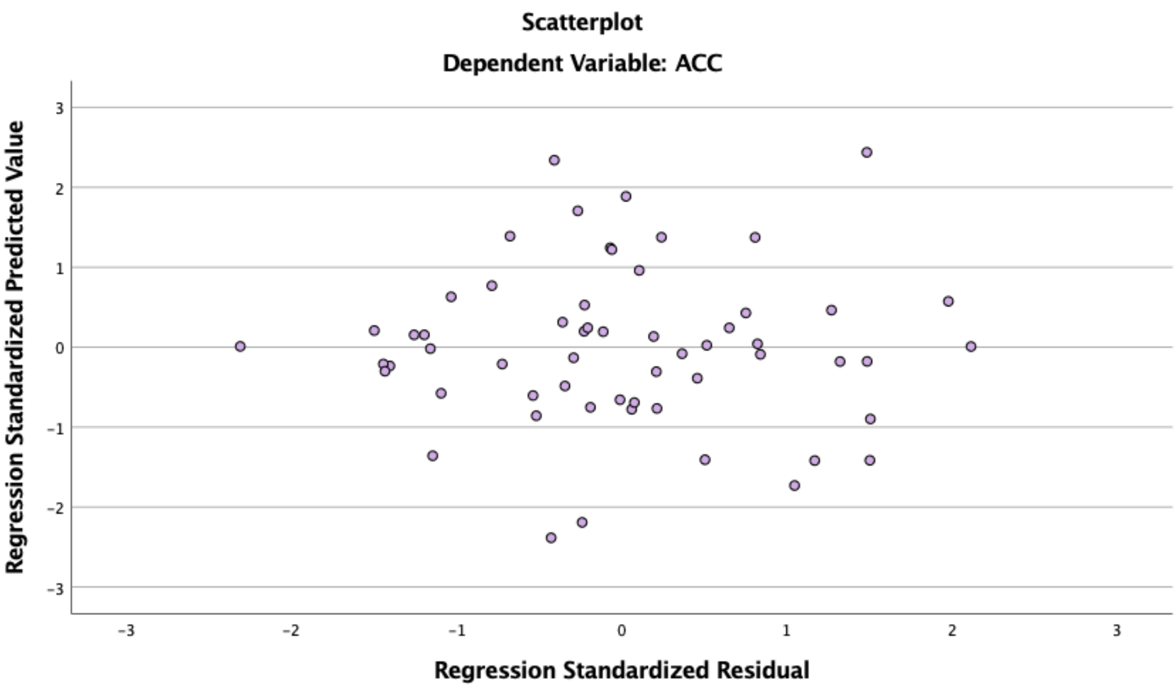


Figure A7

Distribution of the Residuals of Question 2, with Threat and Deprivation as predictors of ACC-activity and Age and Gender as Control Variables.