**A longitudinal study of childhood maltreatment, subcortical development, and subcortico-cortical structural maturational coupling from early to late adolescence**

**Supplementary materials**

# Methods:

Diagram

Description automatically generated **Supplementary Figure S1: Diagram depicting age ranges and measures (symptoms, maltreatment, imaging) taken at each time point between T1 and T5.**

**Interpretation of slopes and maturational coupling**

If both the slope of amygdala growth and PFC thickness were significantly more negative (i.e., flatter amygdala growth and increased PFC thinning), this would represent positive coupling. On the other hand, if the slope of amygdala growth was significantly steeper (relatively more positive; increased growth), while the slope of PFC thickness was steeper (relatively more negative; increased thinning), this would represent negative coupling. See Figure S2 for a visual depiction of positive vs negative coupling classifications in this study.

Chart

Description automatically generated

**Supplementary Figure S2:** **A visual depiction of positive vs negative maturational coupling.** Diagram depicting how positive and negative subcortico-cortical maturational coupling is defined in the present study. Black lines represent the normative trajectory of brain development. Blue lines represent the developmental trajectory associated with maltreatment. Upward and downward arrows represent increases and decreases in development relative to normative development, respectively. Paired relative increases or decreases in development reflect positive maturational coupling. Opposite directions of relative development (i.e., increase and decrease), reflect negative maturational coupling.

## MRI Acquisition parameters:

At baseline, magnetic resonance imaging (MRI) scans were performed at the Brain Research Institute, Melbourne, on a 3-T scanner (repetition time 36 ms, echo time 9 ms, flip angle 35°, field of view 20 cm2; GE Healthcare, Milwaukee, WI, USA) to obtain 124 T1-weighted contiguous slices (i.e., voxel dimensions = 0.4883 × 0.4883 × 1.5 mm). Follow-up scans were conducted at the Royal Children’s Hospital, Melbourne, on a 3-T scanner (repetition time 1,900 ms, echo time 2.24 ms, flip angle 9°, field of view 23 cm2; Siemens Magnetrom TrioTim, Erlangan, Germany), producing 176 T1-weighted contiguous 0.9-mm thick slices (voxel dimensions 0.9 mm3). We have taken several steps to ensure that we used only high-quality data. Each individual’s cortical reconstruction was visually inspected by a trained researcher to ensure that optimal grey/white and grey/cerebrospinal fluid classification had occurred based on differences in tissue intensity signals, and manual edits were made (and edited images re-processed) where necessary to ensure/improve quality of the output. Further, given that different scanners were used at the first vs the second and third MRI assessment, we have previously conduced reliability analyses to address concerns that changes in structure over time may be due to measurement bias from the different scanner platforms and acquisition parameters. These reliability analyses have been described previously (Dennison et al., 2013; Whittle et al., 2017). These analyses did not reveal a systematic bias due to changing scanners.

## Internal consistency (Cronbach α) of BAI and CES-D at each time point

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | T1 | T3 | T4 | T5 |
| BAI | 0.89 | 0.74 | 0.9 | 0.95 |
| CESD | 0.88 | 0.86 | 0.89 | 0.92 |

**Correlation between abuse/neglect and mental health:**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | CESD (T1) | BAI (T1) | CESD (T3) | BAI (T3) | CESD (T4) | BAI (T4) | CESD (T5) | BAI (T5) |
| Abuse | 0.11 (0.37) | 0.15 (0.22) | 0.27 (0.014) | 0.22 (0.06) | 0.11 (0.37) | 0.08 (0.52) | 0.098 (0.36) | 0.11 (0.3) |
| Neglect | 0.18 (0.14) | 0.35 (0.77) | 0.25 (0.027) | 0.08 (0.5) | 0.16 (0.17) | 0.02 (0.93) | 0.16 (.12) | 0.4 (0.74) |

Pearson r (p value) provided in the table

## Number of participants meeting cut-offs for CTQ subscales (as described by Walker et al. (1999)

Number of participants meeting cut-off for:

1. Any of the maltreatment types: 43
2. Physical neglect: 22
3. Physical abuse: 10
4. Emotional neglect: 13
5. Emotional abuse: 20

## Model equations

The (1 | Subject) term represents the random effect of the intercept in each subject. The *e* represents the normally distributed residual error term. Age, sex and IQ were fixed effects in all equations, with β representing the parameter estimates for each of the main effects and interactions. Where we were investigating maltreatment (CTQ) as the predictor, total CTQ/neglect/abuse was used as a fixed effect. Additionally, in maturational coupling analyses, an interaction between CTQ and hippocampus/amygdala random slope was used as a fixed effect. Y and age are time-varying variables, and values for each time point are entered in the model. CTQ refers to total maltreatment, abuse, and neglect – each of which was tested in separate models. All models were run with standardized variables. Lower order effects for each equation containing a 3-way interaction were automatically included. Specific model equations are as follows:

### 3.9.1 Normative models where Y is time-varying variable of amygdala and hippocampus volume (in separate models):

Y = Intercept + (1 | Subject) + β1 (age) + β2 (sex) + βn (covariates) + *e*.

With sex as a moderator:

Y = Intercept + (1 | Subject) + β1 (age) + β2 (sex) + β3(age\*sex) + βn (covariates) + *e*.

### 3.9.2 Subcortical analysis models where Y is time-varying variable of amygdala and hippocampal volume (in separate models):

Y = Intercept + (1 | Subject) + β1(age) + β2(CTQ) + β3(age\*CTQ) + β4(sex) + βn (covariates) + *e*.

With sex as a moderator:

Y = Intercept + (1 | Subject) + β1(age) + β2(CTQ) + β3(sex) + β4(age\*CTQ\*sex) + βn(covariates) + *e*.

### 3.9.3 Maturational coupling models where Y is time-varying variable of PFC thickness (each region in a separate model):

Y = Intercept + (1 | Subject) + β1(age) + β2(CTQ) + β3(amygdala/hippocampus random slope) + β4(age\*CTQ\*amygdala/hippocampus random slope) + β5(sex) + βn (covariates) + *e*.

With sex as a moderator:

Y = Intercept + (1 | Subject) + β1(age) + β2(CTQ) + β3(amygdala/hippocampus random slope) + β4(sex) + β5(age\*CTQ\*amygdala/hippocampus random slope\*sex) + βn (covariates) + *e*.

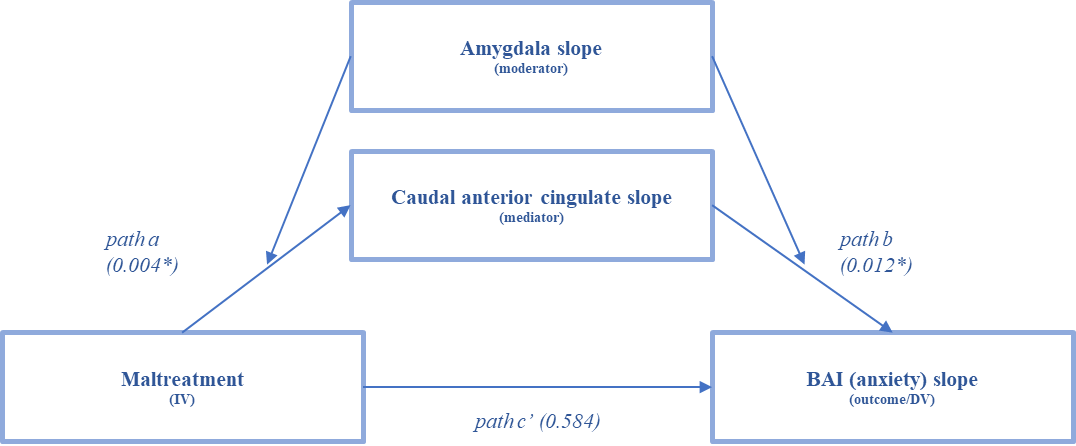
# Diagram Description automatically generatedSupplementary Figure S3: Conceptual mediation model. Diagram depicting mediation analysis with total maltreatment/neglect/abuse as the IV, amygdala/hippocampus slope as the mediator, and symptom slope as the outcome/DV. Path a represents the effect of maltreatment on subcortical slope, path b represents the effect of subcortical slope on symptom slope, and path c’ represents the direct effect between maltreatment and symptom slope.

Diagram

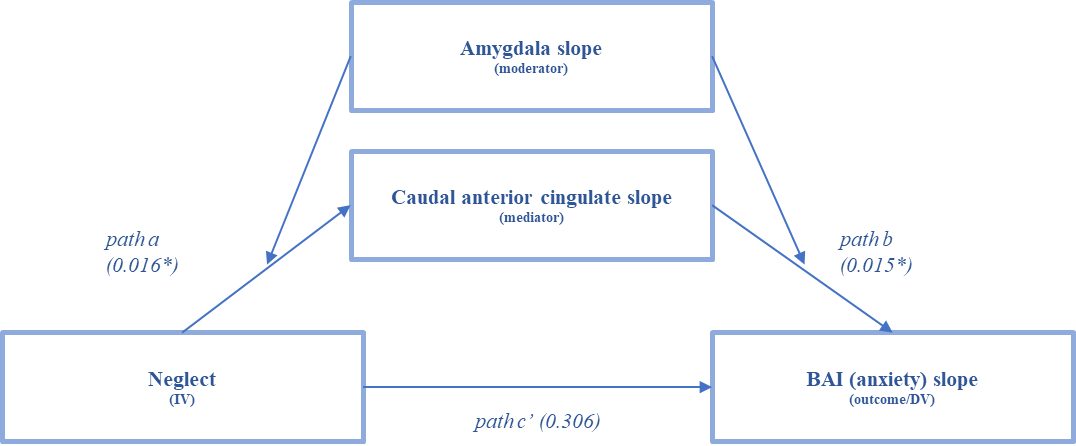
Description automatically generated**Supplementary Figure S4: Conceptual moderated mediation model.** Diagram depicting moderated mediation analysis with total maltreatment/neglect/abuse as the IV, PFC slope as the mediator, amygdala/hippocampus slope as the moderator and symptom slope as the outcome/DV. Path a represents the effect of maltreatment on subcortical slope, path b represents the effect of subcortical slope on symptom slope, and path c’ represents the direct effect between maltreatment and symptom slope.

Diagram

Description automatically generated with medium confidence**Supplementary Figure S5: Normative developmental trajectories of amygdala and hippocampal volume.** (A) Amygdala development in females (p<0.001) and males (p<0.001), and (B) Hippocampal development in females (p = 0.855) and males (p<0.001). Statistics reported in Table 2. Slopes represent average trajectories for males (in dark blue) and females (in light blue). (\* = significant age effect, pFDR < 0.05).



**Supplementary Figure S6: Moderated mediation pathway between neglect, amygdala-caudal anterior cingulate coupling, and anxiety symptoms.** Moderated mediation analysis featuring total maltreatment (IV), amygdala random slope (moderator), caudal anterior cingulate slope (mediator) and BAI slope (outcome/DV). Path a (p = 0.004) depicts the effect of the interaction between neglect and amygdala slope on caudal anterior cingulate slope. Path b (*p* = 0.012) depicts the effect of the interaction between caudal anterior cingulate slope and amygdala slope on BAI slope. Path c’ (*p* = 0.584) illustrates the direct relationship between neglect and BAI slope.



**Supplementary Figure S7: Moderated mediation pathway between neglect, amygdala-caudal anterior cingulate coupling, and anxiety symptoms.** Moderated mediation analysis featuring neglect (IV), amygdala random slope (moderator), caudal anterior cingulate slope (mediator) and BAI slope (outcome/DV). Path a (p = 0.016) depicts the effect of the interaction between neglect and amygdala slope on caudal anterior cingulate slope. Path b (*p* = 0.015) depicts the effect of the interaction between caudal anterior cingulate slope and amygdala slope on BAI slope. Path c’ (*p* = 0.306) illustrates the direct relationship between neglect and BAI slope.

# Results:

# Tables

**Supplementary Table S1: Normative amygdala and hippocampus development**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Dependent variable*** | **Predictor** | **B** | **SE** | **t** | **p** |
| *Amygdala* | Age | 0.17 | 0.02 | 8.82 | < 0.001\* |
| *Hippocampus* | Age | 0.05 | 0.01 | 3.96 | < 0.001\* |
| *Amygdala* | Age x Sex | -0.09 | 0.04 | -2.33 | 0.021\* |
| *Hippocampus* | Age x Sex | -0.1 | 0.026 | -3.92 | < 0.001\* |

\*= pFDR

SE = Standard Error

**Supplementary Table S2: Associations between total maltreatment, neglect and abuse with amygdala/hippocampus development**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Dependent variable*** | **Predictor** | **B** | **SE** | **t** | **p** |
| *Amygdala* | Total CTQ x Age | -0.002 | 0.02 | 0.10 | 0.922 |
|  | Neglect x Age | 0.009 | 0.02 | 0.526 | 0.599 |
|  | Abuse x Age | 0.027 | 0.02 | 1.45 | 0.147 |
| *Hippocampus* | Total CTQ x Age | -0.017 | 0.01 | -1.32 | 0.189 |
|  | Neglect x Age | -0.022 | 0.01 | -1.79 | 0.075 |
|  | Abuse x Age | -0.02 | 0.01 | -1.5 | 0.1337 |
| *Amygdala* | Total CTQ x Age x Sex | 0.052 | 0.04 | 1.46 | 0.146 |
|  | Neglect x Age x Sex | 0.102 | 0.04 | 2.91 | 0.004\* |
|  | Abuse x Age x Sex | 0.034 | 0.04 | 0.91 | 0.365 |
| *Hippocampus* | Total CTQ x Age x Sex | 0.032 | 0.03 | 1.26 | 0.208 |
|  | Neglect x Age x Sex | 0.019 | 0.03 | 0.77 | 0.441 |
|  | Abuse x Age x Sex | 0.04 | 0.03 | 1.49 | 0.138 |

\*= pFDR < 0.05

SE = Standard Error

The effect of neglect x age x sex on amygdala volume was even significant when covarying for estimated total intracranial volume (B = 0.11, SE = 0.04, t = 2.99, p = 0.003).

**Supplementary Table S3: Model output for Associations between total maltreatment and amygdala-PFC maturational coupling (i.e., Total CTQ x Age x Amygdala Random Slope predicting cortical thickness)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Dependent variable (cortical thickness)*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -0.225 | 0.246 | -0.917 | 0.361 |
| *Medial Orbitofrontal* | -0.145 | 0.261 | -0.554 | 0.580 |
| *Pars Opercularis* | 0.086 | 0.227 | 0.380 | 0.705 |
| *Caudal Anterior Cingulate* | 0.597 | 0.190 | 3.136 | 0.002\* |
| *Rostral Middle Frontal* | 0.220 | 0.259 | 0.850 | 0.396 |
| *Caudal Middle Frontal* | -0.089 | 0.286 | -0.311 | 0.756 |
| *Superior Frontal* | 0.326 | 0.245 | 1.331 | 0.185 |
| *Rostral Anterior Cingulate* | -0.209 | 0.256 | -0.817 | 0.415 |
| *Pars Orbitalis* | 0.013 | 0.230 | 0.056 | 0.955 |
| *Pars Triangularis* | -0.067 | 0.248 | -0.269 | 0.788 |
| ***With sex as a moderator*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -1.053 | 0.584 | -1.801 | 0.073 |
| *Medial Orbitofrontal* | -0.811 | 0.623 | -1.302 | 0.195 |
| *Pars Opercularis* | -0.195 | 0.546 | -0.357 | 0.722 |
| *Caudal Anterior Cingulate* | 0.294 | 0.456 | 0.645 | 0.520 |
| *Rostral Middle Frontal* | -0.077 | 0.620 | -0.125 | 0.901 |
| *Caudal Middle Frontal* | -0.233 | 0.686 | -0.340 | 0.734 |
| *Superior Frontal* | -0.022 | 0.583 | -0.038 | 0.970 |
| *Rostral Anterior Cingulate* | -0.456 | 0.614 | -0.743 | 0.458 |
| *Pars Orbitalis* | -0.668 | 0.552 | -1.210 | 0.228 |
| *Pars Triangularis* | -0.482 | 0.585 | -0.823 | 0.412 |

\*= pFDR < 0.05

SE = Standard Error

**Supplementary Tables S4: Model output for Associations between total maltreatment and hippocampus-PFC maturational coupling (i.e., Total CTQ x Age x Hippocampus Random Slope predicting cortical thickness)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Dependent variable (cortical thickness)*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | 1.749 | 1.811 | 0.966 | 0.335 |
| *Medial Orbitofrontal* | 2.703 | 1.908 | 1.416 | 0.158 |
| *Pars Opercularis* | -0.049 | 1.639 | -0.030 | 0.976 |
| *Caudal Anterior Cingulate* | -2.485 | 1.409 | -1.764 | 0.079 |
| *Rostral Middle Frontal* | 2.843 | 1.863 | 1.526 | 0.129 |
| *Caudal Middle Frontal* | 1.428 | 2.066 | 0.691 | 0.490 |
| *Superior Frontal* | 1.328 | 1.756 | 0.756 | 0.451 |
| *Rostral Anterior Cingulate* | 0.153 | 1.885 | 0.081 | 0.936 |
| *Pars Orbitalis* | 1.331 | 1.670 | 0.797 | 0.426 |
| *Pars Triangularis* | -1.017 | 1.758 | -0.578 | 0.564 |
| ***With sex as a moderator*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -0.559 | 4.060 | -0.138 | 0.891 |
| *Medial Orbitofrontal* | 4.394 | 4.220 | 1.041 | 0.299 |
| *Pars Opercularis* | -1.453 | 3.654 | -0.398 | 0.691 |
| *Caudal Anterior Cingulate* | -2.590 | 3.127 | -0.828 | 0.409 |
| *Rostral Middle Frontal* | 4.808 | 4.079 | 1.179 | 0.240 |
| *Caudal Middle Frontal* | 2.501 | 4.606 | 0.543 | 0.588 |
| *Superior Frontal* | 0.110 | 3.834 | 0.029 | 0.977 |
| *Rostral Anterior Cingulate* | -4.838 | 4.226 | -1.145 | 0.254 |
| *Pars Orbitalis* | 5.245 | 3.735 | 1.404 | 0.162 |
| *Pars Triangularis* | -1.840 | 3.906 | -0.471 | 0.638 |

SE = Standard Error

**Supplementary Table S5: Associations between neglect and amygdala-PFC maturational coupling (i.e., Neglect x Age x Amygdala Random Slope predicting cortical thickness)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Dependent variable (cortical thickness)*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -0.326 | 0.204 | -1.602 | 0.111 |
| *Medial Orbitofrontal* | -0.146 | 0.219 | -0.667 | 0.506 |
| *Pars Opercularis* | -0.138 | 0.194 | -0.712 | 0.478 |
| *Caudal Anterior Cingulate* | 0.478 | 0.159 | 2.998 | 0.003\* |
| *Rostral Middle Frontal* | -0.099 | 0.221 | -0.448 | 0.655 |
| *Caudal Middle Frontal* | -0.637 | 0.246 | -2.585 | 0.010 |
| *Superior Frontal* | -0.437 | 0.217 | -2.012 | 0.046 |
| *Rostral Anterior Cingulate* | -0.137 | 0.216 | -0.634 | 0.527 |
| *Pars Orbitalis* | -0.251 | 0.193 | -1.301 | 0.195 |
| *Pars Triangularis* | -0.182 | 0.207 | -0.881 | 0.379 |
| ***With sex as a moderator*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -1.006 | 0.514 | -1.957 | 0.052 |
| *Medial Orbitofrontal* | -0.971 | 0.553 | -1.757 | 0.081 |
| *Pars Opercularis* | -0.566 | 0.492 | -1.150 | 0.252 |
| *Caudal Anterior Cingulate* | -0.196 | 0.409 | -0.480 | 0.632 |
| *Rostral Middle Frontal* | -0.642 | 0.558 | -1.150 | 0.252 |
| *Caudal Middle Frontal* | -0.844 | 0.623 | -1.355 | 0.177 |
| *Superior Frontal* | -1.171 | 0.545 | -2.150 | 0.033 |
| *Rostral Anterior Cingulate* | -0.580 | 0.552 | -1.051 | 0.294 |
| *Pars Orbitalis* | -1.025 | 0.486 | -2.107 | 0.036 |
| *Pars Triangularis* | -0.758 | 0.517 | -1.464 | 0.145 |

SE = Standard Error

**Supplementary Table S6: Model output for associations between neglect and hippocampus-PFC maturational coupling (i.e., Neglect x Age x Hippocampus Random Slope predicting PFC thickness)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Dependent variable (cortical thickness)*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | 1.329 | 1.411 | 0.942 | 0.347 |
| *Medial Orbitofrontal* | 3.762 | 1.478 | 2.546 | 0.012\* |
| *Pars Opercularis* | 1.681 | 1.313 | 1.281 | 0.202 |
| *Caudal Anterior Cingulate* | -3.138 | 1.087 | -2.887 | 0.004\* |
| *Rostral Middle Frontal* | 4.339 | 1.460 | 2.972 | 0.003\* |
| *Caudal Middle Frontal* | 3.348 | 1.667 | 2.008 | 0.046 |
| *Superior Frontal* | 3.935 | 1.439 | 2.735 | 0.007\* |
| *Rostral Anterior Cingulate* | 0.330 | 1.473 | 0.224 | 0.823 |
| *Pars Orbitalis* | 2.498 | 1.301 | 1.920 | 0.056 |
| *Pars Triangularis* | 0.482 | 1.380 | 0.349 | 0.727 |
| ***With sex as a moderator*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -0.294 | 3.174 | -0.093 | 0.926 |
| *Medial Orbitofrontal* | 2.633 | 3.319 | 0.793 | 0.429 |
| *Pars Opercularis* | -0.981 | 2.952 | -0.332 | 0.740 |
| *Caudal Anterior Cingulate* | -1.101 | 2.457 | -0.448 | 0.655 |
| *Rostral Middle Frontal* | 4.201 | 3.239 | 1.297 | 0.196 |
| *Caudal Middle Frontal* | 4.064 | 3.714 | 1.094 | 0.275 |
| *Superior Frontal* | 3.095 | 3.171 | 0.976 | 0.330 |
| *Rostral Anterior Cingulate* | 0.359 | 3.355 | 0.107 | 0.915 |
| *Pars Orbitalis* | 3.495 | 2.946 | 1.187 | 0.237 |
| *Pars Triangularis* | -0.442 | 3.082 | -0.144 | 0.886 |

\*= pFDR

SE = Standard Error

**Supplementary Table S7: Model output for associations between abuse and amygdala-PFC maturational coupling (i.e., Abuse x Age x Amygdala Random Slope predicting PFC thickness)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Dependent variable (cortical thickness)*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -0.287 | 0.253 | -1.134 | 0.258 |
| *Medial Orbitofrontal* | -0.403 | 0.270 | -1.493 | 0.137 |
| *Pars Opercularis* | -0.204 | 0.240 | -0.847 | 0.398 |
| *Caudal Anterior Cingulate* | 0.447 | 0.197 | 2.272 | 0.024 |
| *Rostral Middle Frontal* | -0.061 | 0.272 | -0.225 | 0.822 |
| *Caudal Middle Frontal* | -0.448 | 0.310 | -1.443 | 0.151 |
| *Superior Frontal* | -0.193 | 0.268 | -0.720 | 0.472 |
| *Rostral Anterior Cingulate* | -0.452 | 0.263 | -1.715 | 0.088 |
| *Pars Orbitalis* | -0.169 | 0.240 | -0.706 | 0.481 |
| *Pars Triangularis* | -0.177 | 0.256 | -0.691 | 0.490 |
| ***With sex as a moderator*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -1.097 | 0.708 | -1.549 | 0.123 |
| *Medial Orbitofrontal* | -0.460 | 0.755 | -0.609 | 0.543 |
| *Pars Opercularis* | -0.139 | 0.675 | -0.206 | 0.837 |
| *Caudal Anterior Cingulate* | 1.120 | 0.548 | 2.042 | 0.043 |
| *Rostral Middle Frontal* | -0.118 | 0.758 | -0.155 | 0.877 |
| *Caudal Middle Frontal* | -0.486 | 0.863 | -0.563 | 0.574 |
| *Superior Frontal* | -0.190 | 0.739 | -0.257 | 0.797 |
| *Rostral Anterior Cingulate* | -0.343 | 0.736 | -0.467 | 0.641 |
| *Pars Orbitalis* | -0.800 | 0.672 | -1.190 | 0.235 |
| *Pars Triangularis* | -0.483 | 0.709 | -0.681 | 0.496 |

\*= p < 0.05 but did not survive multiple comparisons

SE = Standard Error

**Supplementary Table S8: Model output for associations between abuse and hippocampus-PFC maturational coupling (i.e., Abuse x Age x Hippocampus random slope predicting PFC thickness)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Dependent variable (cortical thickness)*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | 2.169 | 2.055 | 1.055 | 0.293 |
| *Medial Orbitofrontal* | -2.142 | 2.172 | -0.987 | 0.325 |
| *Pars Opercularis* | -2.406 | 1.910 | -1.260 | 0.209 |
| *Caudal Anterior Cingulate* | 0.353 | 1.600 | 0.221 | 0.826 |
| *Rostral Middle Frontal* | -0.731 | 2.156 | -0.339 | 0.735 |
| *Caudal Middle Frontal* | 1.724 | 2.459 | 0.701 | 0.484 |
| *Superior Frontal* | 1.485 | 2.098 | 0.708 | 0.480 |
| *Rostral Anterior Cingulate* | 2.037 | 2.130 | 0.956 | 0.340 |
| *Pars Orbitalis* | -1.188 | 1.919 | -0.619 | 0.537 |
| *Pars Triangularis* | -3.372 | 1.996 | -1.690 | 0.093 |
| ***With sex as a moderator*** | **B** | **SE** | **t** | **p** |
| *Lateral Orbitofrontal* | -0.288 | 4.954 | -0.058 | 0.954 |
| *Medial Orbitofrontal* | -0.863 | 5.162 | -0.167 | 0.867 |
| *Pars Opercularis* | 0.700 | 4.552 | 0.154 | 0.878 |
| *Caudal Anterior Cingulate* | 0.283 | 3.775 | 0.075 | 0.940 |
| *Rostral Middle Frontal* | 1.685 | 5.046 | 0.334 | 0.739 |
| *Caudal Middle Frontal* | 9.725 | 5.712 | 1.702 | 0.090 |
| *Superior Frontal* | 11.607 | 4.722 | 2.458 | 0.015 |
| *Rostral Anterior Cingulate* | -3.151 | 5.097 | -0.618 | 0.537 |
| *Pars Orbitalis* | 5.982 | 4.592 | 1.303 | 0.194 |
| *Pars Triangularis* | -3.029 | 4.754 | -0.637 | 0.525 |

**Supplementary Table S9: Correlation of random effects during individual random slope extraction**

|  |  |  |
| --- | --- | --- |
| ***Subcortical region*** | **Correlation coefficient** | **Uncorrelated correlation coefficient** |
| *Amygdala* | -0.20 |  |
| *Hippocampus* | 0.93 | 0.13 |
| ***PFC region*** | **Correlation coefficient** | **Uncorrelated correlation coefficient** |
| *Caudal Anterior Cingulate* | 0.006 |  |
| *Caudal Middle Frontal* | 0.46 |  |
| *Superior Frontal* | 0.44 |  |
| *Pars Orbitalis* | -0.54 |  |
| ***Symptom measures*** | **Correlation coefficient** | **Uncorrelated correlation coefficient** |
| *CES-D* | 0.92 | 0.19 |
| *BAI* | 0.46 |  |

*Random effects were extracted to obtain individual random slope values for hippocampal and amygdala growth, as well as for depressive and anxiety symptom trajectories. Where the correlation coefficient of random effects > ±0.9, an uncorrelated correlation coefficient was calculated.*

**Supplementary Table S10: Mediation analysis output testing the influence of amygdala slope as a mediator of the relationship between neglect and anxiety (BAI) and depressive (CES-D) symptoms in females**

|  |  |  |  |
| --- | --- | --- | --- |
| ***Model/Path*** | **b** | **SE** | **p** |
| *Neglect prediction of amygdala slope (path a)* | 0.023 | 0.01 | 0.034\* |
| *Amygdala slope prediction of BAI slope (path b)* | -2.88 | 2.9 | 0.323 |
| *Direct effect of neglect on BAI slope (path c’)* | -0.20 | 0.27 | 0.443 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| *Indirect effect of neglect on BAI slope* | -0.067 | -0.269 | 0.128 |
|  | **b** | **SE** | **p** |
| *Neglect prediction of amygdala slope (path a)* | 0.023 | 0.01 | 0.034\* |
| *Amygdala slope prediction of CES-D slope (path b)* | 0.423 | 1.28 | 0.741 |
| *Direct effect of neglect on CES-D slope (path c’)* | -0.03 | 0.12 | 0.778 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| *Indirect effect of neglect on CES-D slope* | 0.01 | -0.062 | 0.095 |

\*= p < 0.05

SE = Standard Error

BootLLCI = Bootstrap lower level of confidence interval

BootULCI = Bootstrap upper level of confidence interval

**Supplementary Table S11: Mediation analysis output testing the influence of caudal anterior cingulate slope as a mediator of the relationship between total CTQ and anxiety (BAI) and depressive (CES-D) symptoms, moderated by amygdala slope**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **b** | **SE** | **p** |
| Total CTQ x amygdala slope prediction of caudal anterior cingulate slope (path a) | 0.44 | 0.15 | 0.004\* |
| Caudal anterior cingulate slope x amygdala slope prediction of BAI slope (path b) | -23.61 | 9.25 | 0.012\* |
| Direct effect of total CTQ on BAI slope (path c’) | 0.09 | 0.17 | 0.58 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of total CTQ on BAI slope (at -1SD amygdala slope) | -0.20 | -0.45 | < 0.01 |
| Indirect effect of total CTQ on BAI slope (at mean amygdala slope) | -0.02 | -0.12 | 0.07 |
| Indirect effect of total CTQ on BAI slope (at +1SD amygdala slope) | 0.004 | -0.11 | 0.10 |
|  | **b** | **SE** | **p** |
| Total CTQ x amygdala slope prediction of caudal anterior cingulate slope (path a) | 0.44 | 0.15 | 0.004\* |
| Caudal anterior cingulate slope x amygdala slope prediction of CES-D slope (path b) | -3.60 | 4.79 | 0.453 |
| Direct effect of total CTQ on CES-D slope (path c’) | 0.07 | 0.09 | 0.45 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of total CTQ on CES-D slope (at -1SD amygdala slope) | -0.05 | -0.14 | 0.01 |
| Indirect effect of total CTQ on CES-D slope (at mean amygdala slope) | 0.02 | -0.05 | 0.02 |
| Indirect effect of total CTQ on CES-D slope (at +1SD amygdala slope) | 0.02 | -0.03 | 0.07 |

\*= p < 0.05

SE = Standard Error

BootLLCI = Bootstrap lower level of confidence interval

BootULCI = Bootstrap upper level of confidence interval

**Supplementary Table S12: Mediation analysis output testing the influence of caudal anterior cingulate slope as a mediator of the relationship between neglect and anxiety (BAI) and depressive (CES-D) symptoms, moderated by hippocampus slope**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **b** | **SE** | **p** |
| Neglect x hippocampus slope prediction of caudal anterior cingulate slope (path a) | -2.42 | 0.84 | 0.005\* |
| Caudal anterior cingulate slope x hippocampus slope prediction of BAI slope (path b) | 38.19 | 39.29 | 0.333 |
| Direct effect of neglect on BAI slope (path c’) | 0.06 | 0.17 | 0.747 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on BAI slope (at -1SD hippocampus slope) | -0.006 | -0.046 | 0.088 |
| Indirect effect of neglect on BAI slope (at mean hippocampus slope) | 0.003 | -0.094 | 0.047 |
| Indirect effect of neglect on BAI slope (at +1SD hippocampus slope) | 0.018 | -0.260 | 0.212 |
|  | **b** | **SE** | **p** |
| Neglect x hippocampus slope prediction of caudal anterior cingulate slope (path a) | -2.42 | 0.84 | 0.005\* |
| Caudal anterior cingulate slope x hippocampus slope prediction of CES-D slope (path b) | 14.19 | 19.95 | 0.478 |
| Direct effect of neglect on CES-D slope (path c’) | 0.109 | 0.09 | 0.216 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on CES-D slope (at -1SD hippocampus slope) | -0.005 | -0.02 | 0.04 |
| Indirect effect of neglect on CES-D slope (at -mean hippocampus slope) | 0.003 | -0.04 | 0.02 |
| Indirect effect of neglect on CES-D slope (at +1SD hippocampus slope) | 0.018 | -0.11 | 0.02 |

\*= p < 0.05

SE = Standard Error

BootLLCI = Bootstrap lower level of confidence interval

BootULCI = Bootstrap upper level of confidence interval

**Supplementary Table S13: Mediation analysis output testing the influence of superior frontal slope as a mediator of the relationship between neglect and anxiety (BAI) and depressive (CES-D) symptoms, moderated by hippocampus slope**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **b** | **SE** | **p** |
| Neglect x hippocampus slope prediction of superior frontal slope (path a) | 2.41 | 0.81 | 0.004\* |
| superior frontal slope x hippocampus slope prediction of BAI slope (path b) | 13.76 | 44.30 | 0.757 |
| Direct effect of neglect on BAI slope (path c’) | 0.0267 | 0.17 | 0.877 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on BAI slope (at -1SD hippocampus slope) | 0.006 | -0.05 | 0.10 |
| Indirect effect of neglect on BAI slope (at mean hippocampus slope) | 0.003 | -0.03 | 0.05 |
| Indirect effect of neglect on BAI slope (at +1SD hippocampus slope) | -0.02 | -0.13 | 0.11 |
|  | **b** | **SE** | **p** |
| Neglect x hippocampus slope prediction of superior frontal slope (path a) | 2.41 | 0.81 | 0.004\* |
| Superior frontal slope x hippocampus slope prediction of CES-D slope (path b) | -9.38 | 22.36 | 0.676 |
| Direct effect of neglect on CES-D slope (path c’) | 0.098 | 0.09 | 0.266 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on CES-D slope (at -1SD hippocampus slope) | -0.006 | -0.03 | 0.06 |
| Indirect effect of neglect on CES-D slope (at mean hippocampus slope) | 0.003 | -0.02 | 0.03 |
| Indirect effect of neglect on CES-D slope (at +1SD hippocampus slope) | -0.02 | -0.08 | 0.04 |

\*= p < 0.05

SE = Standard Error

BootLLCI = Bootstrap lower level of confidence interval

BootULCI = Bootstrap upper level of confidence interval

**Supplementary Table S14: Mediation analysis output testing the influence medial orbitofrontal slope as a mediator of the relationship between neglect and anxiety (BAI) and depressive (CES-D) symptoms, moderated by hippocampus slope**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **b** | **SE** | **p** |
| Neglect x hippocampus slope prediction of medial orbitofrontal slope (path a) | 1.86 | 0.73 | 0.012\* |
| Medial orbitofrontal slope x hippocampus slope prediction of BAI slope (path b) | -27.50 | 43.67 | 0.53 |
| Direct effect of neglect on BAI slope (path c’) | 0.049 | 0.173 | 0.777 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on BAI slope (at -1SD hippocampus slope) | -0.006 | -0.135 | 0.0473 |
| Indirect effect of neglect on BAI slope (at mean hippocampus slope) | 0.003 | -0.087 | 0.032 |
| Indirect effect of neglect on BAI slope (at +1SD hippocampus slope) | 0.018 | -0.083 | 0.099 |
|  | **b** | **SE** | **p** |
| Neglect x hippocampus slope prediction of medial orbitofrontal slope (path a) | 1.86 | 0.73 | 0.012\* |
| Medial orbitofrontal slope x hippocampus slope prediction of CES-D slope (path b) | -25.93 | 22.07 | 0.242 |
| Direct effect of neglect on CES-D slope (path c’) | 0.11 | 0.09 | 0.223 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on CES-D slope (at -1SD hippocampus slope) | -0.005 | -0.06 | 0.02 |
| Indirect effect of neglect on CES-D slope (at mean hippocampus slope) | 0.003 | -0.03 | 0.02 |
| Indirect effect of neglect on CES-D slope (at +1SD hippocampus slope) | 0.019 | -0.06 | 0.04 |

\*= p < 0.05

SE = Standard Error

BootLLCI = Bootstrap lower level of confidence interval

BootULCI = Bootstrap upper level of confidence interval

**Supplementary Table S15: Mediation analysis output testing the influence of caudal anterior cingulate slope as a mediator of the relationship between neglect and anxiety (BAI) and depressive (CES-D) symptoms, moderated by amygdala slope**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **b** | **SE** | **p** |
| Neglect x amygdala slope prediction of caudal anterior slope (path a) | 0.32 | 0.13 | 0.016\* |
| Caudal anterior slope x amygdala slope prediction of BAI slope (path b) | -21.02 | 8.57 | 0.015\* |
| Direct effect of neglect on BAI slope (path c’) | 0.17 | 0.17 | 0.306 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on BAI slope (at -1SD hippocampus slope) | -0.16 | -0.45 | 0.03 |
| Indirect effect of neglect on BAI slope (at mean hippocampus slope) | -0.02 | -0.13 | 0.07 |
| Indirect effect of neglect on BAI slope (at +1SD hippocampus slope) | 0.01 | -0.08 | 0.1 |
|  | **B** | **SE** | **p** |
| Neglect x amygdala slope prediction of caudal anterior cingulate slope (path a) | 0.32 | 0.13 | 0.016\* |
| Caudal anterior cingulate slope x amygdala slope prediction of CES-D slope (path b) | -3.74 | 4.41 | 0.398 |
| Direct effect of neglect on CES-D slope (path c’) | 0.123 | 0.088 | 0.144 |
|  | **Effect** | **BootLLCI** | **BootULCI** |
| Indirect effect of neglect on CES-D slope (at -1SD hippocampus slope) | -0.044 | -0.14 | 0.01 |
| Indirect effect of neglect on CES-D slope (at mean hippocampus slope) | -0.007 | -0.05 | 0.03 |
| Indirect effect of neglect on CES-D slope (at +1SD hippocampus slope) | 0.009 | -0.02 | 0.07 |

\*= p < 0.05

SE = Standard Error

BootLLCI = Bootstrap lower level of confidence interval

BootULCI = Bootstrap upper level of confidence interval

**Supplementary Table S16: Model outputs of robust linear mixed models for analyses that survived FDR testing**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Dependent variable**  **(subcortical volume)** | **Predictors** | **B** | **SE** | **t** | **p** |
| Amygdala | Neglect x Age | 0.1 | 0.03 | 3.01 | 0.003\* |
| **Dependent variable**  **(cortical thickness)** | **Predictors** | **B** | **SE** | **t** | **p** |
| Caudal Anterior Cingulate | Total CTQ x Age x Amygdala slope | 0.59 | 0.17 | 3.45 | <0.001\* |
| Caudal Anterior Cingulate | Neglect x Age x Hippocampus slope | -3.28 | 0.96 | -3.43 | <0.001\* |
| Medial Orbitofrontal | Neglect x Age x Hippocampus slope | 2.04 | 1.4 | 1.46 | 0.015\* |
| Rostral Middle Frontal | Neglect x Age x Hippocampus slope | 2.32 | 1.46 | 1.59 | 0.011\* |
| Superior Frontal | Neglect x Age x Hippocampus slope | 1.91 | 1.36 | 1.40 | 0.016\* |
| Caudal Anterior Cingulate | Neglect x Age x Amygdala slope | 0.47 | .14 | 3.36 | <0.001\* |

SE = Standard Error

\*= p < 0.05

**Supplementary Table S17: Model outputs of controlling for abuse \* age in significant neglect \*age results and vice versa**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Interaction** | **Dependent variable** | **B** | **SE** | **T** | **P** |
| Neglect \*age | *Amygdala volume* | 0.097 | 0.035 | 2.736 | 0.006 |
| Neglect \* age \* hippocampus random slope | *Medialorbitofrontal\_thickness* | 7.223 | 2.923 | 2.471 | 0.014 |
| *Caudalanteriorcingulate\_thickness* | -6.516 | 2.139 | -3.047 | 0.003 |
| *Rostralmiddlefrontal\_thickness* | 8.362 | 2.881 | 2.903 | 0.004 |
| *Superiorfrontal\_thickness* | 7.400 | 2.810 | 2.633 | 0.009 |
| Neglect \* age \* amygdala random slope | *Caudalanteriorcingulate\_thickness* | 0.455 | 0.159 | 2.855 | 0.005 |

# Exploratory analyses: sex as a moderator

**Results**

A three-way interaction between sex, neglect and age significantly predicted amygdala volume (see Table 1), such that the relationship between neglect and amygdala development was significant in females but not males (Figure S7). In females, higher neglect exposure was associated with relatively increased amygdala development.

Chart

Description automatically generated

**Supplementary Figure S7: Neglect-associated development of amygdala volume.** Amygdala development between the ages of 12 and 19 in (A) females and (B) males. Slopes represent average trajectories for +1SD, mean, and -1SD of total neglect scores. (\* = significant neglect by age interaction, pFDR < 0.05).

**Discussion**

The association between neglect and amygdala development was present in females but not males. This is the first study to examine sex differences in the effects of neglect on longitudinal changes in amygdala volume. Many studies have examined the role of sex in behavioural and socioemotional consequences of neglect (White & Kaffman, 2019), but few have examined its role in neglect-related neurodevelopmental alterations. Cross-sectionally, male-specific adversity-related findings have been reported in several brain regions, including the amygdala (De Bellis & Keshavan, 2003; M et al., 2018; Samplin et al., 2013; Whittle et al., 2016). However, contrary to these cross-sectional findings, our findings suggest that females may be more sensitive to *neurodevelopmental* consequences of maltreatment. While there is a body of literature that supports this notion, particularly following puberty (Bale et al., 2015), sex-specific effects of maltreatment on neurodevelopment are not well understood. Further research is required to understand these underlying mechanisms.