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Research Article

Regional superficial amygdala resting-state functional connectivity in adults infers childhood maltreatment severity

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Abstract

Background: Childhood maltreatment (CM) is a potential risk factor for some neuropsychiatric disorders in adulthood (e.g. depression and anxiety) and alters trajectories of brain development. Accumulating evidence suggests that functional connectivity of the limbic system, especially the amygdala, is highly associated with childhood maltreatment, although not all studies have found this. These inconsistent results may be due to differential alterations of amygdala resting-state functional connectivity (rsFC) following childhood maltreatment.

Objective: Our aim was to investigate the relationship between the rsFC of amygdala subregions and CM severity, as well as to develop a stable rsFC-based model for inferring the severity of CM.

Methods: In this study, we employed the Childhood Trauma Questionnaire (CTQ) to assess CM severity in each individual. We explored the relationship between the rsFC of amygdala subregions (i.e. centromedial -CMA, basolateral -BLA, superficial-SFA amygdala) and CM experience in a discovery dataset of $n = 110$ healthy Chinese participants by linear multiple regression analysis. Subsequent dimensional and categorical approach were performed to elucidate the relationship between rsFCs and CM severity and CM subtypes, respectively. A support vector regression model was then conducted to validate the associations between rsFCs and total CTQ scores. Moreover, we also verified the model into another independent replication dataset ($n = 38$).

Results: Our findings suggested that childhood maltreatment was negatively associated with rsFC between the right superficial amygdala and perigenual anterior cingulate cortex (pgACC)/postcentral gyrus (PCG) but not the other two amygdala subregions. Moreover, SFA-pgACC coupling was more associated with physical neglect whereas the SFA-PCG was more related to emotional neglect. In addition, supervised machine learning confirmed that using these two rsFCs as predictors could stably estimate continuous maltreatment severity in both discovery and replication datasets.

Conclusion: The current study supports that the rsFCs of superficial amygdala are related to childhood maltreatment and which may be a potential biomarker for the effects of childhood maltreatment-related psychiatric disorders (i.e. depression and anxiety).

Keywords: Childhood maltreatment; Amygdala subregions; Superficial amygdala; Resting-state functional connectivity; Neglect

Introduction

Childhood maltreatment (CM), including exposure to abuse and neglect, are stressors and harmful experiences severely impacting on a child's development. CM has been identified as a key contributory factor for neuropsychiatric disorders in adulthood, such as major depressive disorder (MDD), posttraumatic stress disorder (PTSD), anxiety and schizophrenia (Popovic *et al.*, 2019; Yu *et al.*, 2019; Sistad *et al.*, 2021). Some studies have shown that children who experienced multiple forms of maltreatment are three times more likely to suffer mental disorders in adulthood (McKay *et al.*, 2021). Patients with MDD also report higher levels of emotional and physical neglect compared to healthy controls (Frodl *et al.*, 2010a). Meanwhile, a recent meta-analysis study showed that 64.7% of Chinese college students experienced at least one subtype of CM, including emotional, physical, or sexual abuse, as well as physical or emotional neglect, at a mild or higher level (Fu *et al.*, 2018). Converging studies suggest that CM experience is associated with structural or functional changes in specific brain regions (e.g. limbic system; default mode network, DMN; salience network, SN), involved in threat and fear regulation, emotional processing and cognitive control (Sergerie *et al.*, 2008; Maren *et al.*, 2013). Additionally, a relationship between brain findings and specific categories of abuse and neglect was also found. For example, decreases in the volumes of dorsolateral and orbitofrontal cortices, insula and ventral striatum were associated with physical abuse, in the cerebellum with physical neglect, and in dorsolateral, orbitofrontal and subgenual prefrontal cortices, striatum, amygdala, hippocampus and cerebellum with emotional

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neglect in adolescents without psychiatric disorders (Edmiston *et al.*, 2011). Furthermore, hippocampal and striatal alterations in adults have been associated with childhood emotional neglect (Frodl *et al.*, 2010b). Although the severe consequences of CM on brain structure or function have been widely reported (Teicher *et al.*, 2016) using structural or functional magnetic resonance imaging (sMRI or fMRI) techniques, few studies have identified reliable brain-based biomarkers for tracking an individual's CM experience burden.

The amygdala, as a key component of the limbic system, is involved in human social and emotional behaviors (Bos *et al.*, 2013), and plays a crucial role in linking external stimuli to defensive responses (LeDoux, 2003). Recent studies have found that morphometry and functional connectivity of the amygdala may pave a new way in gaining insight into how to understand the neural mechanisms of mental disorders (Teicher and Khan, 2019; Sylvester *et al.*, 2020). Structural magnetic resonance imaging (sMRI) studies have consistently reported that the experience of CM alters the structure of the limbic system, resulting in smaller gray matter volumes in the amygdala and hippocampus (Aas *et al.*, 2012; Paquola *et al.*, 2016). However, resting-state functional connectivity effects of CM have produced inconsistent findings (Teicher and Samson, 2016; Goltermann *et al.*, 2022). Some studies reported a significant negative correlation between CM severity and resting-state functional connectivity (rsFC) between amygdala and cortical regions, such as anterior cingulate cortex (ACC), in both healthy controls and individuals with psychopathology (Birn *et al.*, 2014; Teicher *et al.*, 2016; Popovic *et al.*, 2019), while a recent large-scale study ($n = 701$) did not find this correlation in healthy controls (Goltermann *et al.*, 2022). These inconsistent findings may due to the different functions of amygdala subregions in CM given that the morphometry or rsFC of specific amygdala nuclei improve the accuracy of prediction of psychological disorders compared to the whole amygdala (Saygin *et al.*, 2017; Wang *et al.*, 2021; Phillips *et al.*, 2021; Klein-Flügge *et al.*, 2022).

The anatomical amygdala consists of at least 6 subregions, including left/right centromedial (CMA), basolateral (BLA), and superficial (SFA) amygdala (Roy *et al.*, 2009; Pessoa, 2010). Previous studies have consistently claimed that BLA contributes to the acquisition and elimination of conditioned fear memories (Krabbe *et al.*, 2018), whereas the CMA is more involved in the process of information integration within the amygdala and behavioral response switching (Lei *et al.*, 2015). In addition, only abnormal functional connectivity with CMA was associated with CM experience (Luo *et al.*, 2022a), although significant results were also found in the anatomical structure of the BLA (Giotakos, 2020). While the SFA was originally established to be important for olfactory processing (Heimer and Van Hoesen, 2006), growing evidence extensively has shown its activity to be highly correlated with social information processing as well as emotional regulation (Goossens *et al.*, 2009; Mancke *et al.*, 2018; Luders *et al.*, 2021) given that olfactory input is associated with intraspecific communication and social functioning (Moreno and González, 2007; Bzdok *et al.*, 2013).

Thus, previously the majority of studies have mainly examined the relationship between CM experience and the function or structure of the whole amygdala, rather than its specific subregions (Johnson *et al.*, 2018; Peverill *et al.*, 2019), and this may have produced inconsistent results given that different amygdala subregions are involved in distinct functions. Against this background, the present study aimed: (1) to explore distinct CM effects on these amygdala subregions using rsFC analyses and establishing a rsFC-based model to discriminate CM experience severity in one cohort; (2) to validate the established rsFC-based model in another independent dataset. Thus, we applied subfield-specific amygdala characterization to a resting-state fMRI dataset from $n = 110$ healthy adult male participants, and then employed support vector regression (SVR) to determine whether these rs-FCs could be used to discriminate individual-level CM experience severity. Finally, we evaluated the rsFC-based model in an independent dataset ($n = 38$).

Methods

Participants

Two datasets including high-resolution T1-weighted (T1w) images and resting-state fMRI (rs-fMRI) data were used in the current study: one as discovery data and the other as replication data, respectively.

The discovery dataset included 110 right-handed male Chinese University participants. Two participants were excluded due to head movements > 3 mm and resulted in a total of 108 participants (age range = 18–27 years, mean ± SD = 20.97 ± 2.00 years) in the subsequent analyses. The replication dataset included 92 right-handed Chinese University participants, but only 38 participants (19 males, age range = 18–26 years, mean ± SD = 20.87 ± 2.45 years) completed the required questionnaire within 2–3.5 months after scanning. All participants were recruited via the campus bulletin board system (BBS). None of the participants had any neurological or psychiatric disorders, head trauma, drug, alcohol or cigarette abuse, or MRI contraindications. Both studies were approved by the local ethics committee and were performed in accordance with the latest revision of the Declaration of Helsinki. All participants provided written informed consent before the formal experiment began.

Measurements

The Childhood Trauma Questionnaire Short Form (CTQ-SF) is an extensively validated retrospective questionnaire, and its Chinese version has been demonstrated to be a validated and reliable tool for assessing severity of experienced childhood trauma among Chinese populations (Wang *et al.*, 2020). The questionnaire consists of 25 clinical items (1–5 points for each) and 3 validity items (Bernstein *et al.*, 2003), resulting in five subtypes of trauma: Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, Physical Neglect. The following recommended cutoffs of subtype scores were used to divide participants into CM- (not conform to any standard), CM+ (conform to any standard) and CM++ (conform to two or more standards) subgroups: Emotional Abuse ≥ 9; Physical Abuse ≥ 8; Sexual Abuse ≥ 6; Emotional Neglect ≥ 10; and Physical Neglect ≥ 8 (Pham *et al.*, 2021).

Imaging data acquisition and preprocessing

The following imaging data acquisition and preprocessing procedures were used for both discovery and replication datasets. All participants underwent the resting-state scanning on a 3T GE Discovery MR750 system (General Electric, Milwaukee, WI, USA). High-resolution T1-weighted images were acquired using a spoiled gradient echo pulse sequence: repetition time (TR) = 6 ms; echo time (TE) = 1.964 ms; number of slices = 156; thickness = 1 mm; FOV = 256 × 256 mm^2; flip angle = 9°; matrix = 256 × 256. The scanning parameters for functional images were as followed: repetition time (TR) = 2 000 ms; echo time (TE) = 30 ms; flip angle = 90°; field of view (FOV) = 240 × 240 mm; resolution matrix = 64 × 64; slices = 36; voxel size = 3.1 × 3.1 × 3.8 mm^3. The total resting-state scanning lasted 7 minutes, resulting in 210

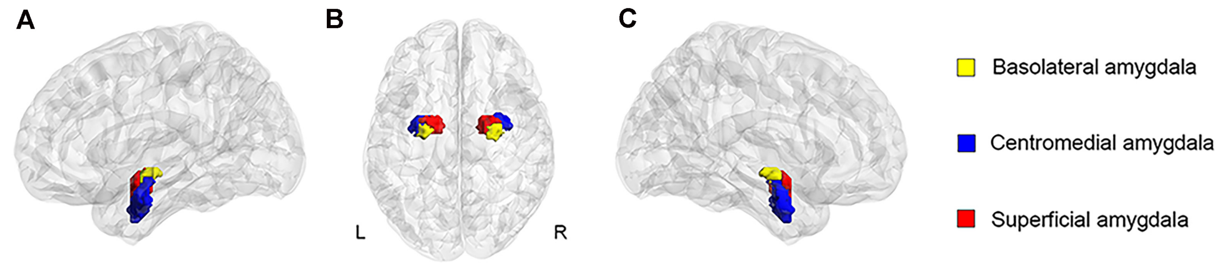

Figure 1: Six regions of interest (ROIs) for rsFC analysis, including the left/right BLA (yellow), CMA (blue) and SFA (red). **a** Left view. **b** Vertical view. **c** Right view.

volumes for each participant. During the scanning, participants were instructed to fixate a white cross centered on a black background and to stay relaxed while not falling asleep. Structural MRI and resting-state fMRI data were processed using fMRIPrep 20.2.1 (Esteban *et al.*, 2019a,b), which is based on Nipype 1.5.1 (Gorgolewski *et al.*, 2011, 2018) (See Supplementary Materials for details).

Statistical analysis and machine learning

ROI-based functional connectivity analysis

To investigate the relationship between amygdala subregions and CM, we firstly defined six subregions of bilateral amygdala including the left/right CMA, BLA and SFA (see Fig. 1) as regions of interest (ROIs) by SPM Anatomy Toolbox 1.8 (Eickhoff *et al.*, 2005; Amunts *et al.*, 2005).

To obtain ROI-based rsFCs, Pearson's correlation coefficients between the mean BOLD signal series of each ROI (i.e. 6 ROIs) and other voxels in the whole brain were calculated, implemented in DPABI v5.2 (Yan and Zang, 2010). We performed Fisher's r-to-z transformation to obtain z-maps with a normal distribution (Cohen *et al.*, 2014). Next, to explore the association between the intrinsic connectivity of amygdala subregions and childhood trauma (CTQ total scores), we performed a whole-brain linear multiple regression analysis using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12) with age as a covariate. For visualization, scatter plot showing the relationship between the extracted values of rsFCs and total CTQ scores was presented. Threshold significance was set at cluster-level $P \leq 0.008$ after false discovery rate (FDR) correction (multiple Bonferroni correction, $P = 0.05/6 = 0.008$).

We extracted the Fisher's z scores of rsFCs with a 6 mm sphere radius at the peak coordinates (Gao *et al.*, 2016; Zhang *et al.*, 2018; Ramot *et al.*, 2019) connected to the amygdala subregions that were significantly correlated with total CTQ scores for subsequent statistical analysis and machine learning. We conducted both dimensional approach (individual variations in CTQ, magnitudes of CTQ scores) and categorical approach (subgroups of CTQ scores, CM-, CM + and CM++) to elucidate the relationship between rsFCs and CM experience as follows: (1) Using a dimensional approach, we performed stepwise linear regression analyses (SPSS 25.0, IBM SPSS Statistics) to further confirm the contribution of each CTQ subscale in theses rsFCs. Stepwise regression is the step-by-step iterative construction of a regression model that involves the selection of CTQ subscales to be used in the final model. (2) Using a categorical approach, we employed one-way ANOVA with CM subgroups (CM-, CM + and CM++) as between-subject factor to examine the differences among the three CM severity sub-groups in the corresponding rsFCs. Bayesian ANOVAs (including post hoc tests) were conducted and BF10 were reported using JASP 0.14.10 (https://jasp-stats.org/), effect sizes using partial eta-squared for F statistics and Cohen's *d* for T statistics were also reported.

Functional connectivity to infer maltreatment severity

To validate our findings, we first trained a support vector regression (SVR, RBF kernel with default parameters, LIBSVM, https://www.csie.ntu.edu.tw/~cjlin/libsvm/) model to estimate CM severity of each participant (estimated CTQ scores) based on the extracted rsFCs values in our discovery cohort ($n = 108$). The leave-one-out-cross-validation (LOOCV, N-1 sets of data are used for model training and 1 set of data is used for model testing, repeated N times) was used for SVR model training and testing. A nonparametric permutation test was conducted to test the significance level of the correlation between the estimated and observed CTQ scores as follows: (1) the CTQ scores were randomly reshuffled among all participants; (2) the same estimation procedure was repeated 5000 permutations;(3) the permutation *p*-value (reliability) was estimated by calculating the percentage of permutations that yield higher estimated -observed correlation values than the estimated -observed correlation based on the original data (Wang *et al.*, 2020).

Moreover, we also verified the generalization of the trained SVR model with an independent dataset ($n = 38$) using the continuous CTQ scores. In brief, the rsFCs of the same positions as the discovery dataset were directly extracted and normalized as inputs of the model to evaluate the individual's CTQ score. Then, the correlation between the estimated and observed CTQ scores was also evaluated.

Results

Demographic information

Descriptive statistical analyses of questionnaires and demographic variables between the discovery dataset (total: $n = 108$; CM-: $n = 25$; CM+: $n = 43$; CM++: $n = 40$) and replication dataset ($n = 38$) were shown in Table 1. There were no significant differences between these two datasets in terms of age, total CTQ scores and CTQ subscales ($P > 0.15$, FDR correction). No significant difference was found in age among three CTQ subgroups (CM-, CM+, CM++).

Functional connectivity of amygdala subregions

In the discovery dataset, the whole-brain rsFC analyses revealed significant negative correlations between total CTQ scores and right SFA-pgACC (perigenual anterior cingulate cortex, cluster size = 28 voxels, peak $MNI_{x,\ y,\ z}$: −4, 44, 6, peak *t* value = 4.75, $p_{uncorr} < 0.001$, $p_{FDR\text{-}corr} = 0.008$) and right SFA- PCG (postcentral gyrus, cluster size = 28 voxels, peak $MNI_{x,\ y,\ z}$: 37, −33, 44,

Table 1: Descriptive: statistics of demographic data.

	Means ± Standard Deviations					Statistical analysis	
	Discovery (n = 108)				Replication		
Variables	CM- (n = 25)	CM+ (n = 43)	CM++ (n = 40)	All (n = 108)	(n = 38)	F/p_{FDR}	T/p_{FDR}
Age (years)	20.88 ± 2.05	21.05 ± 2.07	20.95 ± 1.93	20.97 ± 2.00	20.87 ± 2.45	0.058/0.944	0.259/0.796
Sex	25 males	43 males	40 males	108 males	19 males/ 19 females	–	–
Total Childhood Trauma Questionnaire (CTQ)	27.92 ± 1.89***	33.05 ± 3.01***	41.30 ± 7.08***	34.92 ± 7.12	33.24 ± 6.24	65.222/<0.001	1.290/0.199
- Emotional Abuse	5.52 ± 0.87	5.77 ± 0.87	7.55 ± 2.15	6.37 ± 1.73	6.55 ± 1.74	20.416/<0.001	– 0.559/0.577
- Physical Abuse	5.36 ± 0.70	5.49 ± 0.88	5.25 ± 1.68	5.74 ± 1.26	5.32 ± 0.96	5.705/0.02	1.889/0.214
- Sexual Abuse	5.00 ± 0	5.30 ± 1.26	5.76 ± 1.01	5.33 ± 1.02	5.24 ± 0.88	2.533/0.504	0.517/0.606
- Emotional Neglect	6.40 ± 1.32	9.86 ± 3.34	12.45 ± 3.99	10.02 ± 3.98	8.34 ± 3.35	26.221/<0.001	2.322/0.154
- Physical Neglect	5.64 ± 0.76	6.63 ± 1.62	9.48 ± 2.77	7.45 ± 2.56	7.79 ± 2.74	34.067/<0.001	– 0.683/0.495

F-tests were performed among three subgroups (CM-, CM+, CM++) in the discovery dataset. Independent sample t-tests were performed between discovery dataset and replication dataset, *p* values were adjusted to FDR correction. ***indicates significant differences at $P < 0.001$ among three subgroups.

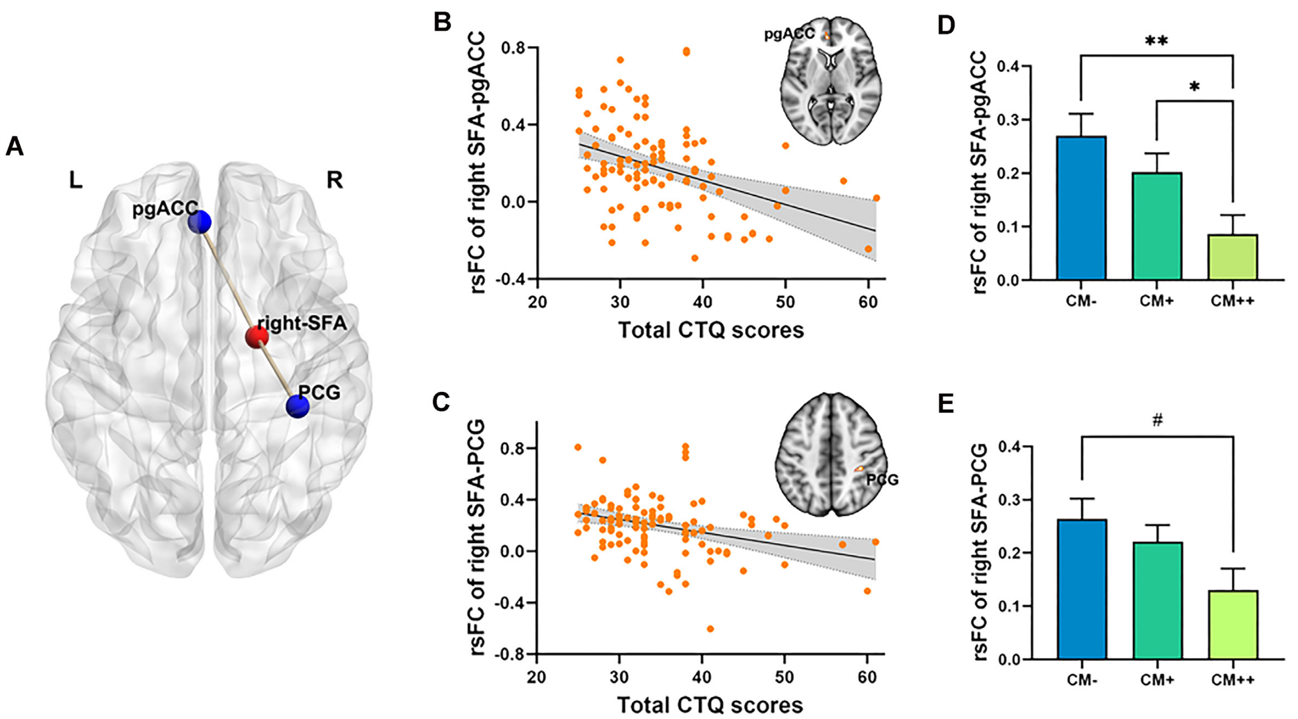

Figure 2: Association between rsFC and Childhood maltreatment severity. **a** Negative correlations with childhood maltreatment were found in right SFA-pgACC (peak $MNI_{x, y, z}$: −4, 44, 6) and right SFA-PCG (peak $MNI_{x, y, z}$: 37, −33, 44). **b-c** The visualized scatter plots show the negative correlation between the total CTQ scores and the rsFC of right SFA-pgACC and right SFA-PCG. **d-e** The box bars show the difference in the rsFC of right SFA-pgACC and right SFA-PCG in childhood maltreatment subgroups (CM-, CM+, CM++). Abbreviations: rsFC: resting-state functional connectivity; SFA: superficial amygdala; pgACC: perigenual anterior cingulate cortex; PCG: postcentral gyrus. Confidence interval (CI), 95%. $^{*}P < 0.05$ FDR correction, $^{**}P < 0.01$ FDR correction, $^{\#}P < 0.05$ uncorrected.

peak *t* value = 3.94, $p_{uncorr} < 0.001$, $p_{FDR\text{-}corr} = 0.008$, Fig. 2a). No significant connectivity results with the other five subregions as seed regions were found at the whole-brain level. Scatter plots showing negative correlation between total CTQ scores and right SFA-pgACC (Fig. 2b) or right SFA-PCG (Fig. 2c) were presented for visualization.

More importantly, stepwise linear regression analysis indicated that physical neglect contributed most in the relationship between CM and right SFA-pgACC coupling (model adjusted $R^2 = 0.123$, $F_{(1\ 106)} = 16.014$, $P < 0.001$, right SFA-pgACC = 0.421–0.033 × physical neglect, Table 2) whereas emotional neglect played crucial role in the regression model of right SFA-PCG coupling (model adjusted $R^2 = 0.058$, $F_{(1\ 106)} = 7.607$, $P = 0.007$, right SFA-PCG = 0.345–0.015 × emotional neglect).

With a categorical approach, one-way-ANOVA also indicated significant differences in CM-, CM + and CM++ subgroups in the rsFCs of right SFA-pgACC ($F_{(2\ 105)} = 5.753$, $P = 0.004$, $\eta^2_p = 0.099$, Fig. 2d) and right SFA-PCG ($F_{(2\ 105)} = 3.159$, $P = 0.047$, $\eta^2_p = 0.057$, Fig. 2e). Specifically, for the rsFC of right SFA-pgACC, post-hoc analysis with FDR correction showed rsFC of CM++ was

Table 2: Linear: regression model using CTQ subscales.

Dependent variables	Predictors	Standardized Coefficients (β)	Statistical values	
			T	*p*
rsFC of SFA-pgACC	**Physical Neglect**	– 0.362	– 4.002	<0.001***
	Emotional Abuse	– 0.177	– 1.828	0.070
	Physical Abuse	– 0.097	– 1.065	0.289
	Sexual Abuse	0.018	0.197	0.084
	Emotional Neglect	– 0.139	– 1.365	0.175
rsFC of SFA-PCG	**Emotional Neglect**	– 0.259	– 2.758	0.007**
	Emotional Abuse	– 0.111	– 1.048	0.297
	Physical Abuse	– 0.204	– 2.204	0.030*
	Sexual Abuse	– 0.052	– 0.547	0.585
	Physical Neglect	– 0.114	– 1.074	0.285

Linear regression model results from discovery dataset indicating the contribution of five subscale scores (physical/emotional neglect, emotional/physical/sexual abuse) for two functional connectivity (superficial amygdala (SFA) -perigenual anterior cingulate cortex (pgACC)/-postcentral gyrus (PCG)) separately. Statistic (both unstandardized and standardized coefficients β values) and p values for linear regression model analysis. $^{**}P < 0.01$, $^{***}P < 0.001$.

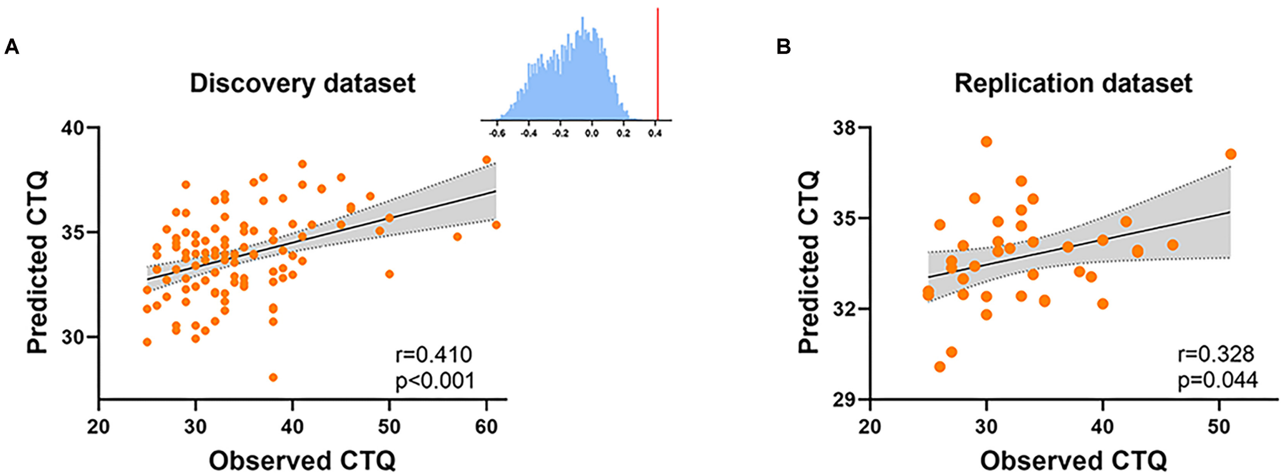

Figure 3: Functional connectivity can predict CTQ scores in both discovery dataset and replication dataset. **a** Functional connectivity of right SFA can predict total CTQ scores in discovery dataset. The blue histogram represents the distribution of correlation coefficients obtained from 5000 permutation tests, and the red line represents the original correlation coefficient. **b** The model of discovery dataset can be used to predict total CTQ scores for replication dataset. Abbreviations: CTQ: Childhood trauma questionnaire; SFA: superficial amygdala. Confidence interval (CI), 95%.

significantly lower than CM+ ($t_{(81)} = 2.313$, Cohen's $d = 0.64$, $p_{FDR} = 0.036$, BF10 = 2.270) and CM- ($t_{(63)} = 3.297$, Cohen's $d = 0.84$, $p_{FDR} = 0.005$, BF10 = 20.662), while right SFA-PCG couple in CM++ was decreased than CM- ($t_{(63)} = 2.237$, Cohen's $d = 0.57$, $p_{uncorrected} = 0.029$, BF10 = 2.055) but not CM+ ($t_{(81)} = 1.782$, $P = 0.078$).

Functional connectivity as an estimation of childhood maltreatment severity

To confirm the robustness of these observed rsFCs, we first trained an SVR model with the discovery dataset using these two rsFC values as predictors and total CTQ scores as labels. Using LOOCV, we found that both right SFA-pgACC and right SFA-PCG could significantly estimate the participants' total CTQ scores (mean average error, MAE = 4.837, $r = 0.410$, $P < 0.001$, 5000 permutation tests Fig. 3a). At the same time, right SFA-pgACC and right SFA-PCG could also estimation physical neglect (MAE = 1.844, $r = 0.359$, $P < 0.001$, 5000 permutation tests) and emotional neglect (MAE = 3.161, $r = 0.241$, $P = 0.003$, 5000 permutation tests), respectively. In addition, we also tested this in an independent replication dataset and consistent estimated results of CTQ (MAE = 4.977, $r = 0.328$, $P = 0.044$, Fig. 3b) were found.

Discussion

The present study aimed to investigate the underlying relationship between CM and the resting-state functional connectivity of amygdala subregions and examine whether the strength of functional coupling could stably estimate CM scores through supervised learning. Our findings demonstrated that CM was only negatively correlated with the intrinsic connectivity between the right superficial amygdala (SFA) and perigenual anterior cingulate cortex (pgACC)/postcentral gyrus (PCG), which is engaged in emotion regulation and somatosensory information processing in adulthood (Hakamata *et al.*, 2017; Zhang *et al.*, 2022), but not associated with other amygdala subregions. The CM induced alterations in these pathways may contribute to increased vulnerability for psychiatric disorders in individuals exposed to adverse childhood experience. More importantly, SFA-pgACC coupling was more associated with physical neglect whereas SFA-PCG coupling was more related to emotional neglect, suggesting distinct functions of these two pathways. Furthermore, the severity of CM can be consistently strongly estimated by a SVR model with two independent datasets suggesting a highly generalizable effect. These findings revealed the underlying mechanism by which CM impairs the functional network of amygdala subregions, and provides a possible clinical utility for the diagnosis, prognosis, and potential treatment selection of related psychiatric disorders (i.e. PTSD and anxiety).

Our neural results showed that CM experience significantly correlated with the resting-state functional connectivity of right SFA in adulthood, with lower connectivity strength being associated with worse CM experience, consistent with both animal models and human studies. Rodent studies have found that early life stress disrupted fear recall and fear conditioning circuits involving the amygdala, medial prefrontal cortex (mPFC) and hippocampus (Ishikawa *et al.*, 2015; Lesuis *et al.*, 2019). For humans, adverse childhood experiences consistently reduced the functional connectivity of amygdala in adulthood (Herringa *et al.*, 2013; Fan *et al.*, 2014). However, the results for amygdala subregions remain controversial. Accumulating evidence suggested that SFA is involved in emotional and social information processing, especially fear (Goossens *et al.*, 2009; Bzdok *et al.*, 2013). Specifically, the activation of SFA was significantly higher than other amygdala subregions in response to emotional face stimuli (i.e. fearful expressions) compared with non-social stimuli, and fear-evoking music stimulated the SFA more than joy-evoking music (Goossens *et al.*, 2009; Skouras *et al.*, 2014). In addition, recent studies have shown atypical functional connectivity in the SFA in internalizing psychiatric disorders (such as PTSD and anxiety) associated with child maltreatment (Wang *et al.*, 2021; Leite *et al.*, 2022). Taken together, these studies suggested that adverse childhood experiences may affect emotions, especially fear information processing circuits, by reducing functional connectivity in the SFA, which in turn predisposes individuals to psychiatric disorders in adulthood.

Interestingly, the effect of adverse childhood experiences was only found on the rsFC of the right but not the left SFA. Although previous studies on the lateralization of CM effects have been inconsistent (Barker *et al.*, 2016; Ahmed-Leitao *et al.*, 2016), more and more studies support CM influencing the structure or function of the right amygdala more (Veer *et al.*, 2015; Fowler *et al.*, 2021). A recent study found that the functional connectivity of right amygdala-mPFC was positively associated with child emotion regulation ability and negatively correlated with child negative affect (Gaffrey *et al.*, 2021). We supposed that the association of the rsFC of the right SFA with CM in this study may reflect adverse childhood experiences altered brain functional activity in childhood which persists into adulthood.

Given that the pgACC, one important node in the salience network, plays a pivotal role in emotion processing, especially emotion regulation and emotional conflicts, and anxiety (Egner *et al.*, 2008; Hakamata *et al.*, 2017; Korgaonkar *et al.*, 2021), it is not surprising that the coupling of right SFA and pgACC was negatively associated with childhood trauma, in particular with physical neglect. One previous study on bipolar disorder supported that the functional connectivity between the ventromedial prefrontal cortex (vmPFC, which includes the pgACC) and the limbic system (amygdala and hippocampus) was negatively associated with emotional and physical neglect (Souza-Queiroz *et al.*, 2016). Although one study claimed that the functional connectivity of vmPFC-amygdala when viewing negative pictures was more negative in abuse-exposed adolescents compared with ones with no history of maltreatment and correlated with abuse severity (Peverill *et al.*, 2019), we did not find any significant associations with childhood abuse. This may be due to relatively low scores of abuse in healthy adult college students based with the reported proportion of college students exposed to physical and sexual abuse being only 17.4% and 15.7% (Fu *et al.*, 2018). Overall, functional uncoupling of the right SFA-pgACC associated with CM may lead to impaired regulation of negative emotions and inability to extinguish fear responses.

On the other hand, emotional neglect contributed more to the FC between right SFA and PCG. The PCG, as primary somatosensory cortex, is involved in perceptual proprioception and emotion regulation (Kropf *et al.*, 2018). Childhood trauma, especially emotional neglect, is associated with volume reductions in a neural emotional regulation system including frontal regions, amygdala and hippocampus (Sinha *et al.*, 2004), and trauma also leads to abnormal fALFF in PCG (Luo *et al.*, 2022b). Similarly, healthy individuals who were depressed during the COVID-19 pandemic exhibited reduced functional connectivity between the amygdala and PCG (Zhang *et al.*, 2022). However, Blair *et al.*, 2019 only observed the extent of adolescent abuse was associated with reduced activity in the postcentral gyrus, rather than neglect, during an affective Stroop task. Above all, CM, especially physical and emotional neglect, may alter two different pathways and then impact the development of the emotional regulation system, thereby further increasing risk for the development of mood disorders.

There are some limitations in our current study. Firstly, lateralization of the amygdala may be related to gender and age (Schneider *et al.*, 2011; Clewett *et al.*, 2014; Lungu *et al.*, 2015) even though no studies to date have reported significant gender differences in childhood trauma (Fu *et al.*, 2018; Nogovitsyn *et al.*, 2022). We only included male participants in the discovery dataset and the current findings should be validated in both genders. Further studies should also consider the effects of age on CM. Secondly, our current findings were from healthy controls and more clinical studies, especially some CM-related psychiatric disorders (i.e. PTSD, depression, etc.), should be explored to confirm the reliability of these two pathways as biomarkers. Finally, there was a gap (i.e. 2–3.5 months) between questionnaire data collection and scanning in the replication dataset, however CTQ as a retrospective questionnaire has a good replicability (Jiang *et al.*, 2018) and thus the time gap should have only had minimal effects on scores. In addition, the current replication sample size is relatively small although some previous studies with a small sample found a highly generalizable effect (Zhou *et al.*, 2020, 2021).

In conclusion, the current study supports the specific involvement of SFA in the impact of childhood maltreatment on brain function in adulthood. Importantly, the resting-state functional connectivity of right SFA-pgACC is more associated with physical neglect whereas that of the right SFA-PCG with emotional neglect. Overall, these two functional pathways can be used as predictors to consistently and stably estimated the severity of adverse childhood experiences. Therefore, our findings may provide reliable neural biomarkers for childhood maltreatment-related psychiatric disorders.

Supplementary Data

Supplementary data is available at *PSYRAD Journal* online.

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Conflict of Interest

The authors report no conflict of interest.

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Data Availability

Data and code used in the present study can be made available upon request to the primary contact author.

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