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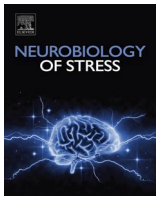

Cross-sectional study of retrospective self-reported childhood emotional neglect and inhibitory neurometabolite levels in the pregenual anterior cingulate cortex in adult humans

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ABSTRACT

High childhood emotional maltreatment (CM-EMO) is reported in mood and anxiety disorders. The associations with an increased risk for psychopathology are not fully understood. One potential factor may be through alterations in gamma-Aminobutyric acid (GABA). The pregenual anterior cingulate cortex (pgACC) is an important brain region for emotion processing and its' GABA levels were previously implicated in mood and anxiety disorders pathophysiology. We examined the association between the self-reported CM-EMO in adulthood and GABA + levels in the pgACC and in a control region, anterior mid cingulate cortex. GABA+ and total creatine (tCr) were measured in the pgACC and aMCC voxels in seventy-four healthy volunteers (32 (43%) women, ages 19–54, age [standard deviation] = 27.1 [6.5]) using proton magnetic resonance spectroscopy at 7 T. Childhood Trauma Questionnaire was completed by adult participants to measure retrospective self-reported experience of emotional neglect (CM-EMO-NEG) and emotional abuse (CM-EMO-AB) during childhood. Linear mixed models tested the interaction between the region and the two subscales, and GABA+/tCr ratios, with an adjusted alpha = 0.025. Following, linear models, including with covariates were tested. There was an interaction effect between region and CM-EMO-NEG ($B = -0.007$, $p = 0.009$), driven by a negative relationship between CM-EMO-NEG and GABA+/tCr in the pgACC ($B = -0.004$, $p = 0.013$). Results for CM-EMO-NEG were robust to inclusion of different covariates (ps < 0.035). There was no interaction effect for the CM-EMO-AB ($B = 0.007$, $p = 0.4$). Limitations include cross-sectional measurement and retrospective nature of the CTQ. The findings indicate preliminary importance of inhibitory neurometabolite concentrations in the pgACC for retrospective reporting of CM-EMO-NEG.

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1. Introduction

Childhood emotional maltreatment (CM-EMO) is a prevalent form of childhood maltreatment (CM) with high rates in the general population worldwide (Rehan et al., 2017; Schulz et al., 2014). CM-EMO includes emotional neglect (CM-EMO-NEG) and emotional abuse (CM-EMO-AB). CM-EMO-NEG is broadly defined as an incident or a pattern of failure of a caregiver to provide for child's emotional and safety needs and development, while CM-EMO-AB is defined as incidents or patterns of non-physical forms of intentional rejection and hostility (World Health Organization, 2006; Gilbert et al., 2009). Studies investigating retrospective self-reported CM-EMO have indicated that both CM-EMO-NEG and CM-EMO-AB are highly prevalent in mood (Nelson et al., 2017; Struck et al., 2020) and anxiety disorders (Gardner et al. 2019), increase the risk for developing these disorders (Li, D'Arcy, and Meng 2016), but are also the least studied forms of childhood maltreatment (Lippard and Nemeroff 2020). A recent meta-analysis that focused on the retrospective reports using Childhood Trauma Questionnaire also showed that the CM-EMO-NEG and CM-EMO-AB were highly related to depression (Humphreys et al., 2020).

The hypothesized long-term impact of CM-EMO, measured with self-reporting questionnaires, has been connected with alterations in brain structure and function (Cassiers et al., 2018). Reviews of structural and functional magnetic resonance imaging (MRI) studies implicated alterations in limbic, prefrontal cortex and pregenual anterior cingulate cortex (pgACC) related to both CM-EMO-NEG and CM-EMO-AB (Teicher et al., 2016). The pgACC is highly implicated in processing of emotional content (Marusak et al., 2016; Etkin et al. 2011), specifically negative stimuli (Coen et al., 2009). Importantly, alterations in structure and function of the pgACC were also connected to mood and anxiety symptoms and disorders (Janiri et al., 2020, Shin and Liberzon, 2010) indicating regional convergence with CM-EMO. Reduced volume of the pgACC has been associated with mood and anxiety disorders (Lai 2013; Konarski et al., 2008; Shang et al., 2014) disorders, as well as altered functional activity and connectivity (Horn et al., 2010; Blumberg et al., 2003; Anand et al., 2009). The neural features of the pgACC have been also proposed as predictors of treatment improvement (Chen et al., 2007; Godlewska et al., 2018).

Structural and functional neuroimaging are useful in detecting macroscopic brain alterations, while proton magnetic resonance spectroscopy (^{1}HMRS) may be used to detect subtle alterations in neurometabolite composition of the brain before large changes in brain anatomy or physiology occur (Ross and Bluml 2001). ^{1}HMRS allows *in vivo* measurement of neurometabolites in a predefined region (Ross and Bluml 2001), which may provide insight into neurobiological correlates of CM-EMO and following pathophysiological processes (Malhi et al., 2002). High field ^{1}HMRS may be particularly useful, as it allows quantification of γ-aminobutyric acid (GABA) (Godlewska et al., 2017). GABA is a neurometabolite implicated in mood and anxiety disorders in humans (Möhler 2012; Kalueff and Nutt 2007). Moreover, animal models of early life affective deprivation showed reductions in the GABAergic system in prelimbic prefrontal cortex, encompassing homologue area to human pgACC (Ohta et al., 2020) and adult anxiety-like phenotypes (Wang et al., 2020), suggesting a potential link between the CM-EMO, reduced inhibitory neurometabolite levels in adult animals and mood and anxiety disorders. However, the relationship in humans has not been tested so far since studies investigating associations between neurometabolites and any type of CM in healthy volunteers or participants with psychiatric disorders are few and focused on neurometabolites other than GABA (Averill et al., 2020; Sonmez et al., 2021; Milani et al., 2018; Duncan et al., 2015; Kim et al., 2019; Stevens et al., 2016; Bio et al., 2021; Raparia et al., 2016; Poletti et al., 2016).

In this cross-sectional study, the associations between the retrospective self-reported CM-EMO-NEG and CM-EMO-AB measured with the Childhood Trauma Questionnaire (Bernstein et al., 2003) and the pgACC GABA levels measured with a 7 T scanner were tested. We hypothesized a negative association between both facets of CM-EMO and GABA levels in the pgACC.

2. Materials and methods

2.1. Participants

The study included one hundred and eight healthy volunteers (47 (43.5%) women; ages 19–54, mean age± standard deviation (SD) = 27.1 ± 6.4), recruited through advertisement to participate in two studies. Data were pooled across two studies to obtain a larger sample, and part of participants did not fill out CTQ-SF (Supplementary Table S1). Participants were asked to note their "Geschlecht", a term interchangeably used for sex and gender. Participants were assessed with the German Version 5.0.0 of the Mini International Neuropsychiatric Interview (M.I.N.I.) (Ackenheil et al., 1999; Sheehan et al., 1998), to ensure the absence of current and lifetime psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (First et al., 1994). Participants were without medication (excluding contraception pills for women), determined by the medical history interview. Other exclusion criteria were neurological illness, other major medical illness (e.g., diabetes) and magnetic resonance (MR) contraindications. All participants were right-handed, measured with the short form of the Edinburgh Handedness Inventory (Oldfield 1971). Medical history interview and examination were done by a study physician. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Magdeburg. All participants gave written informed consent and were reimbursed for their participation.

2.2. Assessment of emotional neglect and abuse

Participants completed a basic demographic interview. Out of the initial study cohort, seventy-eight participants filled out the German version of the short form of the Childhood Trauma Questionnaire (CTQ-SF) (Bernstein et al., 2003; Wingenfeld et al., 2010). The CTQ-SF is a self-report questionnaire that assesses five types of negative childhood experiences: physical, emotional, and sexual abuse and physical and emotional neglect. Each scale consists of five items rated with a five-point Likert scale ranging from 1 (never true) to 5 (very often true), and severity scores range from 5 to 25. Reliability, validity, and item consistency have been demonstrated for the German version of the CTQ (Klinitzke et al., 2012). The study focused on the emotional neglect (CM-EMO-NEG) and the emotional abuse (CM-EMO-AB) scales for analysis.

2.3. Magnetic resonance data acquisition and analysis

Participants completed a structural and ^{1}HMRS scanning on a 7 T MR scanner with a 32-channel head array coil (Siemens Healthineers, Erlangen, Germany). Participants were scanned between 10.30 h and 16.30 h. High resolution structural T1-weighted images were measured with a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence and following parameters: echo time (TE) = 2.73 ms, repetition time (TR) = 2300 ms, inversion time (TI) = 1050 ms, flip angle = 5°, bandwidth = 150 Hz/pixel, acquisition matrix = 320 × 320 × 224, isotropic voxel size = 0.8 mm. ^{1}HMRS was measured with a stimulated-echo acquisition mode (STEAM) sequence and the following parameters: TE = 20 ms, TR = 3000 ms, mixing time (TM) = 10 ms, bandwidth = 2800 Hz, and number of excitations = 128. A single-average water signal served as the internal reference for quantification and eddy-current correction. Spectra were acquired with a 10 × 20 × 15 mm^3 voxel placed in the pgACC (Fig. 1) and in a control voxel with a 25 × 15 × 10 mm^3, the aMCC (Supplementary Fig. S1). For each participant, the ^{1}HMRS voxels was placed manually by the same experienced technician (RBL) in an anatomically defined region to avoid signal contamination

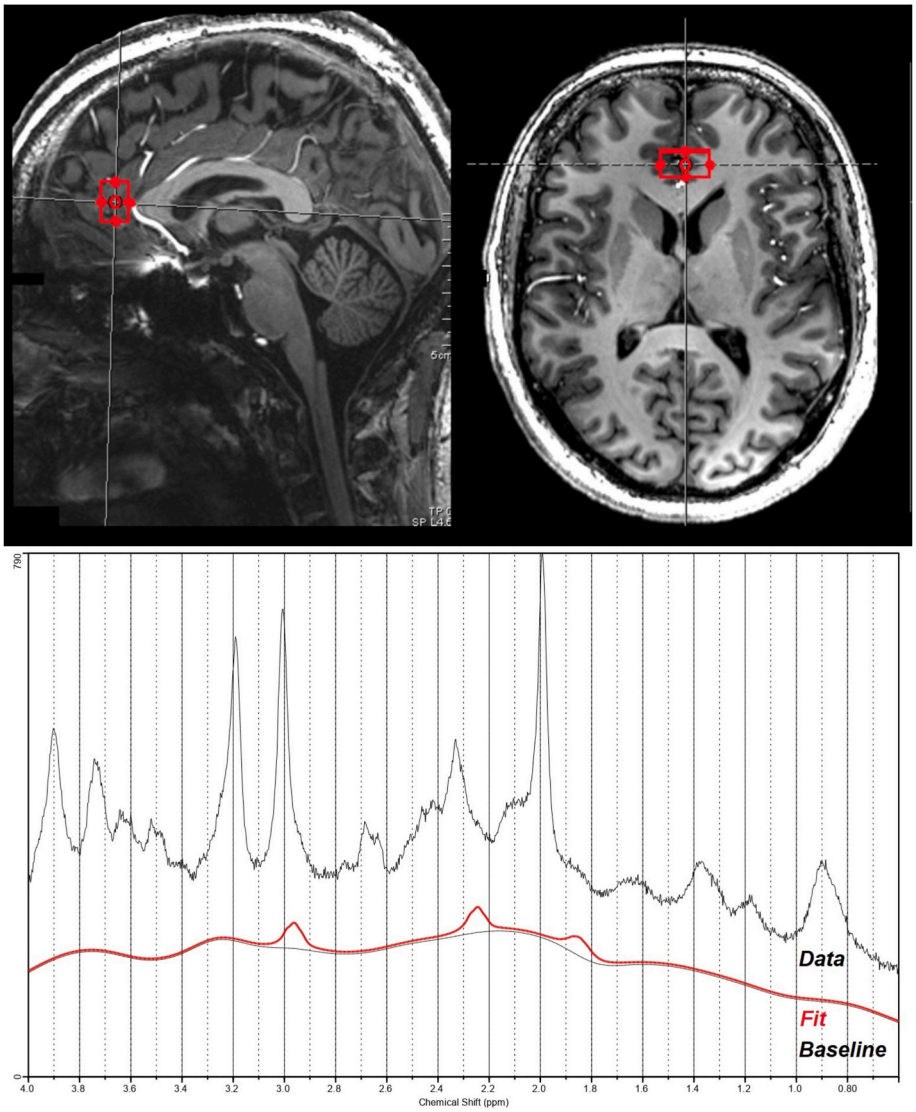

Fig. 1. [1]HMRS voxel position in the pgACC for one participant (upper panel). Example edited spectra for GABA + for one participant (lower panel).
Abbreviations: GABA = Gamma-Aminobutyric acid; pgACC = pregenual Anterior Cingulate Cortex.
Fig. 1 **Alt Text**: Upper panel photograph shows a sagittal and axial section of the structural brain image and the proton magnetic resonance spectroscopy voxel placement in the pregenual anterior cingulate cortex that is shown as a red square touching the genu of the corpus callosum and encompassing Brodmann areas 24 and 32.
Lower panel shows fitted line of the edited spectra in red, raw data in black and baseline in light gray. The three peaks of GABA neurometabolites are visible on the spectra. X-axis shows chemical shift in ppm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

by the callosomarginal artery, and for pgACC encompassing bilateral Brodmann areas 24a, 24b and 32 (Dou et al., 2013).

Spectral data (0.6–4.0 ppm) were fitted and quantified using LCModel (V6.3.0; Stephen Provencher, Inc., Oakville, Canada) (Provencher 2001) with a sequence-specific basis-set. The basis set was measured in the same scanner and metabolites included neurometabolites of interest, GABA+ (a sum of GABA and coedited macromolecules), creatine and phosphocreatine (tCr), and control neurometabolites N-acetylaspartate (NAA), and choline and phosphocholine (tCho). Positioning of the voxels was examined (LC) and all voxels were placed correctly. Spectra were excluded based on visual inspection of the curve fit (LC), or if the Cramér Rao lower bounds (CRLB) > 20%, full width at half maximum >24 Hz, or signal-to-noise ratio <20. An exemplary spectrum of GABA+ is shown in Fig. 1. Individual structural images were segmented to gray matter, white matter, and cerebrospinal fluid using VBM (www.neuro.uni-jena.de/vbm) in SPM12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). The proportion of gray matter, white matter, and cerebrospinal fluid within the individual pgACC voxels were calculated with the help of segmentation, and the gray and white matter proportion was used as covariate of no interest in follow-up models. Ratio of GABA + to tCr were used in all analyses and are reported in institutional units. TCr is a stable neurometabolite and is thus often used as a reference molecule (Godlewska et al., 2017). To confirm that the observed association were due to GABA+ and not tCr, control models were done with GABA+/NAA and GABA+/tCho.

2.4. Statistical analysis

Analyses and graphics were done in R (R Version 3.6.3, (Team 2016)). To examine whether CM-EMO-NEG or CM-EMO-AB impacted GABA+/tCr in a region-specific manner, namely in the pgACC, we used linear mixed models. GABA/tCr were analyzed as a function of CM-EMO-NEG or CM-EMO-AB and region (pgACC vs aMCC). Participants were considered as a random effect and random intercept was estimated. Mixed models were estimated using Satterthwaite approximate degrees of freedom and estimates were obtained by restricted maximum likelihood estimation. Models had an unstructured variance-covariance matrix. Normality of the variance was checked via residual plots. The alpha value was set to 0.025 to account for two scales. Linear mixed models (with diagnostics and plotting) were run with 'lme4', 'lmerTest', 'sjPlot', 'multilevelTools' and 'car', while graphs with 'ggplot2' packages. Following significant interaction effect, two main linear regression models with GABA+/tCr as dependent and CM-EMO-NEG or CM-EMO-AB as independent variables were tested. Supporting models with age, sex, and CSF proportion were tested, and

model fits were compared to the baseline model. Linear model assumptions (global stat, skewness, kurtosis, link function and heteroscedasticity) were verified using the 'gvlma' package (Peña and Slate 2006) and variance inflation factor (VIF< 10) was tested using 'car' package (Fox et al., 2012). In the case of violation of assumptions, robust linear regressions were used (MASS package (Ripley et al., 2013)) to confirm results. To test whether coefficients of CM-EMO-NEG and CM-EMO-AB are significantly different from each other for GABA+/tCr in the pgACC, a single model was run, and coefficients were compared with 'car' package. To confirm the effects were due to GABA+ and not tCr, mixed models and following linear models were ran with GABA+/NAA and GABA+/tCho. Additionally, we tested associations of pgACC tCr/tNAA and tCr/tCho with CM-EMO-NEG. As sensitivity analyses, we detected the outliers for CM-EMO-NEG and CM-EMO-AB using the Rosner test ('EnvStats' package) and ran the individual linear models without the outliers.

3. Results

Out of seventy-eight participants that filled the CTQ-SF questionnaire and completed 7 T ^{1}HMRS scan, four were excluded for incomplete questionnaires for either subscale while nine for insufficient spectroscopy data quality for the pgACC and twenty-one for aMCC. Table 1 summarizes descriptive characteristics of the whole sample that had filled out CTQ-SF, while Supplementary Table S1 shows subsamples characteristics.

For the CM-EMO-NEG there was a significant interaction effect with the region (B = −0.007, p = 0.009) which was not present for the CM-EMO-AB (B = −0.001, p = 0.6; Table S2). Follow-up analysis revealed that high CM-EMO-NEG was associated with low GABA+/tCr in the pgACC (R^2 = 0.09, adjusted R^2 = 0.08, p = 0.013; B = −0.004, 95%CI [−0.008, −0.001], p = 0.013; Fig. 2), and not aMCC (R^2 = 0.01, adjusted R^2 = −0.005, p = 0.4; B = 0.002, 95%CI [−0.003, 0.008], p = 0.4). Since linear model did not satisfy model assumptions (global stats and skewness), to confirm results a robust linear model was run which confirmed the negative association between the CM-EMO-NEG and GABA+/tCr (F = 5.68, p = 0.02). Inclusion of further covariates (age, sex and CSF proportion) to the model did not improve the fit (Fs < 1.61, ps > 0.21), so the covariates were dropped for parsimony. Models' statistics are summarized in Table S3.

Table 1
Descriptive statistics of the study variables (number of participants = 74).

	Range	Mean [SD]
Age	19–54	27.1 [6.5]
Sex	32 women (43.2%)	
CM-EMO-NEG	5–19	8.4 [3.1]
CM-EMO-AB	5–21	7.2 [2.9]
pgACC ^{1}HMRS data[a]		
SNR	33–55	44 [5.5]
FWHM	0.01-0.04	0.02 [0.007]
SD (GABA+) (%)	5–16	8.7 [2.2]
SD (tCr) (%)	4–8	5.4 [1.0]
GABA+/tCr	0.10-0.31	0.18 [0.05]
CSF proportion	0.69-0.97	0.88 [0.05]
aMCC ^{1}HMRS data[b]		
SNR	27–56	43.1 [5.8]
FWHM	0.01-0.06	0.02 [0.009]
SD (GABA+) (%)	4–14	9 [2.1]
SD (tCr) (%)	3–8	4 [0.8]
GABA+/tCr	0.09-0.35	0.19 [0.06]
CSF proportion	0.80-0.99	0.92 [0.04]

Abbreviations: aMCC = anterior mid cingulate cortex; CSF proportion = Proportion within the measured voxel without the cerebrospinal fluid; CM-EMO-AB = subscale Emotional Abuse of the Childhood Trauma Questionnaire; CM-EMO-NEG = subscale Emotional Neglect of the Childhood Trauma Questionnaire; FWMH= Full Width at Half Maximum; GABA+ = sum of Gamma-Aminobutyric acid and coedited macromolecules; MRS = Magnetic Resonance Spectroscopy; pgACC = pregenual Anterior Cingulate Cortex; SD= Standard Deviation; SNR= Signal to Noise Ratio; tCr = total Creatine.
[a] available for sixty-five participants.
[b] available for fifty-three participants.

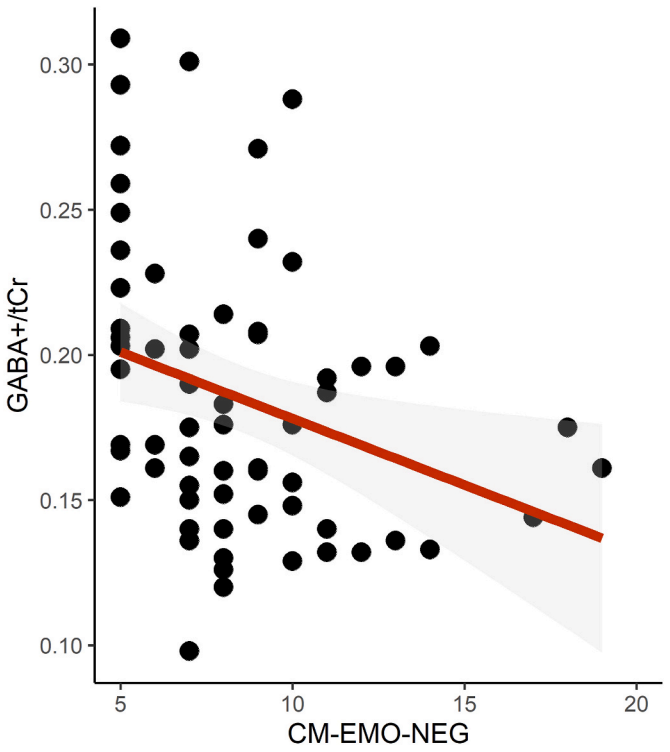

Fig. 2. Linear association between the CM-EMO-NEG and GABA+/tCr in the pgACC (B = −0.004, 95%CI [-0.008, −0.001], p = 0.013). Shaded area represents 95% confidence interval around the mean.
Abbreviations: CM-EMO-NEG = subscale Emotional Neglect of the Childhood Trauma Questionnaire; GABA+/tCr = sum of Gamma-Aminobutyric acid and coedited macromolecules divided by total Creatine.
Fig. 2 **Alt Text**: Figure shows a scatterplot with a fitted linear negative line in dark orange and 95% confidence intervals in light gray. X-axis denotes childhood trauma questionnaire emotional neglect scale and y-axis denotes neurometabolic ratio of GABA + to total creatine. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In contrast, CM-EMO-AB was not significantly associated with GABA+/tCr in the pgACC (R^2 = 0.01, adjusted R^2 = −0.003, p = 0.38; B = −0.002, 95%CI [−0.006, 0.002], p = 0.38). Models did not satisfy model assumptions (skewness). Thus, a robust linear model was run, and CM-EMO-AB was not significant (F = 0.63, p = 0.43). Including covariates to the model did not improve the fit (Fs < 1.88, ps > 0.18). The joined model with CM-EMO-NEG and CM-EMO-AB showed that the coefficients significantly differed from each other (F = 4.11, p = 0.047).

Analysis with the other ratios (GABA+/NAA and GABA+/tCho) showed same regional and scale specificity (Table S4). TCr/NAA (B = 0.004, 95%CI [−0.004, 0.01], p = 0.31) and tCr/tCho (B = 0.02, 95%CI [−0.04, 0.09], p = 0.4) did not display significant associations. Sensitivity analysis without outliers revealed similar results (Table S5).

4. Discussion

CM-EMO and alterations in GABA levels were independently connected with mood and anxiety disorders pathophysiology in adult humans, and animal models suggest that the effects of CM-EMO may be a consequence of the altered GABAergic system in adult animals. This cross-sectional study thus investigated the association between the retrospective self-reported CM-EMO and GABA+/tCr levels in the

pgACC, and control region aMCC measured with a 7 T MR in adult healthy participants. The main finding of the study was that the CM-EMO-NEG was negatively associated with the GABA+/tCr levels in the pgACC and this result was robust to inclusion of covariates and choice of models, while the CM-EMO-AB did not show significant associations. Our findings suggest that the CM-EMO-NEG and altered neurometabolite levels in a region that is implicated in mood and anxiety disorders pathophysiology are interconnected.

Previous studies, also cross-sectional in nature, which investigated associations between neurometabolites and CM examined various regions (voxels) and neurometabolites, other than GABA, measured at lower field strength of 3 T. Four of them found associations in healthy adult participants. Duncan et al. (2015) reported a negative association between the CTQ total score and glutamate/N-acetylaspartate in the medial prefrontal cortex (encompassing part of pgACC), while Kim et al. (2019) reported a negative association between the parental verbal abuse scores and myo-inositol in a voxel encompassing pgACC and medial prefrontal and medial orbitofrontal cortex. Raparia et al. (2016) described a negative association between the CM-EMO-AB and N-acetylaspartate, creatine and choline across multiple regions (rostral prefrontal, motor and sensorimotor cortices) using proton magnetic resonance spectroscopic imaging (^{1}HMRSI). A preliminary investigations that focused on children and adolescents reported a negative association between the CTQ total score and N-acetylaspartate/Glx levels in the pgACC across healthy and individuals with mood disorder (Sonmez et al., 2021). Taken together, research highlights those different forms of CM are connected to altered neurometabolite levels in multiple brain regions in healthy participants, suggesting neurobiological alterations that may pose a risk factor for the alterations in brain function. In particular, the altered glutamate (Duncan et al., 2015; Bio et al., 2021) and GABA levels (reported here) in the pgACC may influence brain connectivity (Martens et al., 2020; Horn et al., 2010; Pizzi et al., 2017) and emotion processing (Denzel et al., 2020; Northoff et al., 2007).

Literature supports the connection between the retrospective self-reported CM-EMO-NEG and depression and anxiety symptoms in adults (Van Veen et al., 2013; Mandelli et al. 2015; Humphreys et al., 2020). Moreover, altered GABA + levels were previously connected to risk factors for mood and anxiety disorders, e.g., harm avoidance (Colic et al., 2018), trait anxiety (Rosso et al., 2014), impaired cognitive emotional awareness (Kühnel et al., 2020), and perceived stress (Strasser et al., 2019). Together, at least in adults there may be a connection between self-reported CM-EMO-NEG, GABA + levels in the pgACC and risk factors for mood and anxiety disorders. We speculate that the link between CM-EMO-NEG and GABA + levels may be viewed as a latent vulnerability in healthy populations (McCrory et al. 2017) or as resilience defined “ex post facto” as suggested by (Kalisch et al., 2017). In this view resilience is understood as “a good mental health outcome following an adverse life event or a period of difficult life circumstances.” Given our healthy sample despite reported CM-EMO, we might have observed a resilience factor. Due to the cross-sectional design, we cannot make any statement about resilience predictors and the dynamic adaptation to maltreatment. We thus assume CM-EMO-NEG to be an important factor to control and examine when investigating GABA + levels in participants with anxiety and mood disorders.

Contrary to our hypothesis, self-reported CM-EMO-AB did not associate with GABA/tCr levels in the pgACC, and in a joint model, coefficients between CM-EMO-AB and -NEG differed significantly. There may be differences between the two facets despite a theoretical overlap and co-occurrence. Some authors highlight the difference denoting CM-EMO-NEG as "maltreatment by omission" and CM-EMO-AB as "maltreatment by commission" (Infurna et al., 2016). It may be plausible that the two facets are related to brain structure and function in distinct ways (McLaughlin et al. 2014). We speculate that experiences of "omission" may shape social and valence expectancy processes linked to activations in the pgACC (Somerville et al. 2006; von Düring et al., 2019; Grimm et al., 2009). On the other hand, experiences of "commission" may shape valence assessment and aversion processes and related regions (e.g., amygdala and dorsal frontal cortex) (Peverill et al., 2019; Blair et al., 2019). However, due to the retrospective nature of our study we cannot exclude that there are biases in reporting different facets of maltreatment (Feldman-Summers and Pope 1994), although this seems more specific for sexual abuse (Gibb et al. 2003; Williams 1994), which was not investigated here.

There are some limitations to this study. Foremost, the study was cross-sectional, and we only used the CTQ-SF, which is a retrospective self-report questionnaire. Due to the cross-sectional design no statement on causality could be made. It remains an open research question whether CM-EMO-NEG prospectively alters GABA + levels during development to adulthood in pgACC and whether this alteration is stable over time in adulthood. While retrospective self-reports of CM are stable over time (Cay et al., 2022; Simpson et al., 2019; Goltermann et al., 2022), there is a lack of long-term (e.g., >2 years) longitudinal human imaging studies that would measure GABA level stability and alterations during development. Dynamic processes in the GABAergic system during perinatal and early postnatal period are indicated by animal studies (Cellot and Cherubini 2013; Ben-Ari 2002), as well as by a rare human positron emission imaging study across development (Chugani et al., 2001). This makes GABAergic system malleable to salient environmental events such as CM-EMO. Moreover, we used only one retrospective self-report questionnaire to measure CM-EMO. Addition of another questionnaire measuring exposure to maltreatment would have strengthen the confidence in the observed maltreatment type associations, also given the gap in some psychometric properties of the CTQ-SF (Georgieva et al. 2021). The small effects size also warrants future investigations that will ideally include multiple assessments of MRS and maltreatment questionnaires. As in most ^{1}HMRS studies, there are potential confounds in the neurometabolite quantification. To mitigate, the study used high field strength of 7 T where signal dispersion is increased, which facilitates the separation of GABA + peaks from overlapping resonances. Moreover, to avoid unreliable measurements ^{1}HMRS data was included using stringent criteria. Another important limitation of the study is lack of the control for the menstrual phase or the exact type of hormonal contraception for the women participants. It is suggested that the GABA levels fluctuate within the cycle or are affected by hormonal intake (De Bondt et al., 2015; Epperson et al., 2006; Spurny-Dworak et al., 2022). Future studies should ideally incorporate multiple measures of GABA+ and CTQ-SF across the cycle to test the robustness of the association. Previous research also indicated that CTQ-SF scores might be affected by gender bias in response due to different interpretation of the single items (Rodriguez et al., 2018), although the differences seemed more relevant for physical subscales (Wright et al., 2001). Since our study did not focus on physical subscales or gender differences, we only considered gender as a covariate of no interest.

This study and analyses were not pre-registered. To obtain a sufficiently large sample, data were pooled and sample size was comparable to other samples that investigated implication of GABA+ in psychiatric disorders (Schür et al., 2016). The study was limited in power to find association between the GABA+ in the aMCC or with CM-EMO-AB (*post-hoc* power analysis is supplementary material). There were also limited distributions of the CM-EMO-NEG and CM-EMO-AB scores as our study cohort were young healthy participants. Future studies should include participants with severe scores of the self-reported CM-EMO--NEG (i.e., ≥18) and CM-EMO-AB (i.e., ≥16), including also participants with mood or anxiety disorders. Given the speculated link to psychopathology of anxiety and mood disorders, a comparison to individuals with mood or anxiety disorders could have provided initial indications as to whether altered GABA + levels are a marker of latent vulnerability or of resilience. Future studies should also include additional tests, e.g., stress or emotional task to further disentangle the interaction of GABA+

and CM-EMO-NEG on a behavioral level.

5. Conclusions

Our results indicate that the self-reported CM-EMO-NEG is negatively associated with the inhibitory neurometabolite GABA+/tCr measured in the pgACC, an area implicated in emotion processing, and in which altered neurometabolism and function has been reported in mood and anxiety disorders. Future longitudinal studies should aim to clarify the robustness and stability of the observed association, ideally throughout the development to adulthood.

Data availability statement

Due to data protection laws processed data is available from the authors upon reasonable request. The data that support the findings of this study are available from the corresponding author (LC).

Authorship

Luisa Hermann: Formal analysis, Visualization, Writing - Original Draft, Johanna Ade: Writing - Original Draft, Anne Kühnel: Formal analysis, Data Curation, Writing - Review & Editing Annina Widmann: Data Curation, Writing - Review & Editing Liliana Ramona Demenescu: Investigation, Writing - Review & Editing Meng Li: Formal analysis, Data Curation, Writing - Review & Editing; Nils Opel: Writing - Review & Editing, Oliver Speck: Methodology, Writing - Review & Editing; Martin Walter: Conceptualization, Funding acquisition, Writing - Review & Editing; Lejla Colic: Investigation, Conceptualization, Writing - Review & Editing. All authors gave the final approval of the version to be submitted.

Declaration of competing interest

MW is a member of the advisory boards and gave presentations for the following companies: Boehringer Ingelheim, Germany; Bayer AG, Germany; and Biologische Heilmittel Heel GmbH, Germany. MW has further conducted studies with institutional research support from HEEL and from Janssen Pharmaceutical Research for a clinical trial (IIT) on ketamine in patients with major depression unrelated to this investigation. MW has not received any financial compensation from above-mentioned companies. All other authors report no conflict of interest.

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Appendix A. Supplementary data

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