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Childhood maltreatment results in altered deactivation of reward processing circuits in depressed patients: A functional magnetic resonance imaging study of a facial emotion recognition task

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ABSTRACT

Importance and objectives: Childhood adversity is a strong risk factor for the development of various psychopathologies including major depressive disorder (MDD). However, not all depressed patients experience early life trauma. Functional magnetic resonance imaging (fMRI) studies using facial emotion processing tasks have documented altered blood-oxygen-level-dependent (BOLD) responses in specific cortico-limbic networks both in MDD patients and in individuals with a history of childhood maltreatment (CM). Therefore, a history of maltreatment may represent a key modulating factor responsible for the altered processing of socio-affective stimuli. To test this hypothesis, we recruited MDD patients with and without of maltreatment history to study the long-term consequences of childhood trauma and examined the impact of CM on brain activity using a facial emotion recognition fMRI task.

Methods: MDD patients with childhood maltreatment (MDD + CM, $n = 21$), MDD patients without maltreatment (MDD, $n = 19$), and healthy controls ($n = 21$) matched for age, sex and intelligence quotient underwent fMRI while performing a block design facial emotion matching task with images portraying negative emotions (fear, anger and sadness). The history of maltreatment was assessed with the 28-item Childhood Trauma Questionnaire.

Results: Both MDD and MDD + CM patients displayed impaired accuracy to recognize sad faces. Analysis of brain activity revealed that MDD + CM patients had significantly reduced negative BOLD signals in their right accumbens, subcallosal cortex, and anterior paracingulate gyrus compared to controls. Furthermore, MDD + CM patients had a significantly increased negative BOLD response in their right precentral and postcentral gyri compared to controls. We found little difference between MDD and MDD + CM patients, except that MDD + CM patients had reduced negative BOLD response in their anterior paracingulate gyrus relative to the MDD group.

Conclusions: Our present data provide evidence that depressed patients with a history of maltreatment are impaired in facial emotion recognition and that they display altered functioning of key reward-related fronto-striatal circuits during a facial emotion matching task.

1. Introduction

Exposure to neglect and abuse in childhood is highly prevalent and represents a global moral and health problem (Gilbert et al., 2009; Bellis et al., 2014). Approximately 30–50% of the adult population experience at least one form of adverse childhood experience (Felitti et al., 1998; Kessler et al., 2010; Vanaelst et al., 2012). Childhood maltreatment

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Abbreviations

BOLD	blood-oxygen-level-dependent
CTQ	childhood trauma questionnaire
CM	childhood maltreatment
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
HC	healthy control
IQ	intelligence quotient
MDD	major depressive disorder
PFC	prefrontal cortex
PTSD	post-traumatic stress disorder

(CM) is a potent risk factor for the development of a wide spectrum of physical and mental disorders and can eventually lead to premature mortality (Felitti et al., 1998; Anda et al., 2006; Gilbert et al., 2009; Brown et al., 2009; Carr et al., 2013; Hughes et al., 2017). Individuals with a history of adverse experiences display altered structural and functional brain development of cortico-limbic circuits (Pechtel and Pizzagalli, 2011; Dannlowski et al., 2012; Hart and Rubia, 2012; Lim et al., 2014; Teicher et al., 2016; Teicher and Samson, 2016). Furthermore, a history of childhood trauma elicits a host of biological responses which in turn significantly increase the risk to develop depressive disorders later in adulthood (McLaughlin et al., 2010; Heim and Binder, 2012). Among others, disturbed functioning of the hypothalamic-pituitary-adrenal axis (van Bodegom et al., 2017) and altered inflammatory responses (Danese and Lewis, 2017) have been pointed out as key mechanisms, while more recently, epigenetic modifications like methylation, histone modifications, and the role of small noncoding RNAs (microRNAs) have emerged as potential contributors to the maladaptive processes associated with early life trauma (Heim and Binder, 2012; Torres-Berrío et al., 2019; Allen and Dwivedi, 2020).

Major depressive disorder (MDD) is a common and heterogeneous mental disorder with complex and not fully understood pathophysiology (Otte et al., 2016). Besides depressed mood, anhedonia, and cognitive symptoms such as self-focused attention, self-referential thinking, as well as impaired social behavior hallmark the clinical feature of MDD. All types of child maltreatment are considered as significant risk factors for MDD in adults (meta-analyzed by Mandelli et al., 2015; Li et al., 2016; Humphreys et al., 2020). Emotional abuse and neglect have the strongest association with the prevalence of MDD, although the different types of maltreatments typically co-occur. Moreover, child maltreatment is associated with the occurrence of chronic, as well as a recurrent course of MDD, and can predict poor treatment response and outcome (Nanni et al., 2012).

Neuroimaging methods have been extensively employed to study the neurobiological underpinnings of MDD (Anderson et al., 2020). Deficits in emotional processing are one of the most obvious clinical symptoms of MDD, and neuroimaging studies document altered functioning of neural circuitries underlying these emotional impairments (Li and Wang, 2021). A large body of human data from functional and structural imaging studies as well as postmortem histopathological evidences indicate that a neural circuitry which connects the medial prefrontal cortex to limbic structures such as the amygdala, and to subcortical structures like the ventral striatum and pallidum, the medial thalamus, and hypothalamus, forms a neural network system which is centrally involved in mood disorders (Price and Drevets, 2010; Zhang et al., 2013; Helm et al., 2018). Furthermore, a recent meta-analysis which analyzed neuroimaging studies investigating reward processing functions in MDD reported that dysregulated corticostriatal connectivity may explain the reward-processing abnormalities in MDD (Ng et al., 2019).

Functional magnetic resonance imaging (fMRI) is a well-established method to investigate the activity of cortico-limbic as well as reward-related fronto-striatal neural circuits in depressed individuals (Hamilton et al., 2012; Zhang et al., 2013). In fMRI studies, facial emotion processing paradigms are widely used to examine functional brain abnormalities in MDD patients. Typically, depressed patients display exaggerated amygdala activation in response to faces expressing negative emotions (Sheline et al., 2001; Dannlowski et al., 2007; Peluso et al., 2009; Victor et al., 2010; Palmer et al., 2015). However, exaggerated amygdala responses to negative facial expressions have also been reported in patients with post-traumatic stress disorder (PTSD) (Shin et al., 2005) and in healthy individuals who experienced childhood maltreatment (Dannlowski et al., 2012, 2013). Since a significant percentage of patients with MDD has been exposed to early life trauma, former neuroimaging investigations could be confounded by this variable. Some of the neurobiological alterations found in MDD patients could be accredited to the difference in the history of childhood maltreatment (Hart and Rubia, 2012). In support of this concept, childhood maltreatment has also been associated with enhanced bilateral amygdala reactivity to emotional faces in general (van Harmelen et al., 2013) and with greater activation of the prefrontal cortex and basal ganglia and increased amygdala connectivity with the hippocampus and prefrontal cortex during a facial emotion recognition task (Jedd et al., 2015; Demers et al., 2018). In addition to that, studies investigating maltreated individuals document disturbed functioning of lateral and ventromedial fronto-limbic networks which mediate affect control (Hart and Rubia, 2012). More recently, a hypothesis has been put forward proposing that childhood maltreatment results in diminished inhibition of the amygdala by the medial PFC during emotional processing and the consequent hyperactivity of the amygdala may constitute a vulnerability marker for depressive symptoms in later life (Kessler et al., 2020). Therefore, it is important to understand the contribution of CM, as a key moderating variable, to the pathophysiology of neural networks regulating higher-order socio-cognitive processes in patients with depressive disorders. Indeed, a robust positive correlation has been found between physical childhood abuse and right amygdala response to sad face stimuli in depressed patients suggesting that the relationship between childhood trauma and risk for depression might be mediated by heightened amygdala responses to negative stimuli (Grant et al., 2011; Kessler et al., 2020).

To further examine neurobiological correlates of childhood maltreatment in adult patients with MDD, we designed an fMRI study, where we investigated the influence of childhood maltreatment on the neural processing of negative socio-affective stimuli in patients with MDD. We compared the blood-oxygen-level-dependent (BOLD) responses of three groups of participants using an established facial emotion recognition fMRI paradigm: 1) MDD patients who experienced severe to extreme maltreatment; 2) MDD patients who were exposed to moderate childhood maltreatment at most and 3) healthy, never-depressed controls. We decided to use a well-established face matching emotional fMRI task, because this task reliably activates brain areas involved in emotional processing (e.g. the amygdala) (Costafreda et al., 2008; Sergerie et al., 2008). Furthermore, this task has been subjected to thorough scrutiny (McDermott et al., 2018) and recommended for between-subject designs (Plichta et al., 2012). Several studies employed this task and demonstrated that adults with a history of CM react differently and show greater brain activation when they perform this task (Bérubé et al., 2021). For socio-affective stimuli, we used photographs of faces expressing negative emotions: fear, anger, and sadness. We used images of negative emotions because evidence suggests that negative emotional stimuli activates the amygdala with higher probability (Costafreda et al., 2008), and because individuals with a history of early adversity react to sad faces with heightened bilateral amygdala activity compared to other facial emotions (Saarinen et al., 2021). Furthermore, it has been reported that abused children have a recognition bias for negative expressions, and that neglected children have a shorter reaction time for recognition of negative facial expressions (Assed et al., 2020).

We hypothesized that depressed patients with a history of childhood maltreatment will perceive such negative socio-affective stimuli as more arousing and threatening and will display different brain activity patterns compared to controls and also to MDD patients. To certify this hypothesis, we compared the activation and deactivation patterns of neural circuits during the facial emotion matching task in the control, MDD, and MDD + CM groups. We also evaluated interactions and correlations of the BOLD responses with the clinical data.

2. Material and methods

2.1. Subjects

Forty patients with major depressive disorder and 21 age-, sex- and education matched healthy controls (HC) participated in the study. We set the following exclusion criteria for participation: current substance use (i.e. abstinence for <2 years), history of internal medical or neurological disorders, head injury, hearing or visual impairment, an Intelligence Quotient (IQ) < 85, and any MR scanning issues (e.g. claustrophobia, or metal objects in the body). Moreover, no participants exposed to traumatic life events fulfilling the DSM-5 PTSD criterion A were enrolled in the study.

Patients with major depression (N = 40) were recruited from the Affective Disorder Unit of the Department of Psychiatry and Psychotherapy, University of Pécs. All patients fulfilled the DSM-5 diagnostic criteria of major depression (American Psychiatric Association, 2013), assessed using the Structured Clinical Interviews for DSM-5 disorders (SCID-5-CV and SCID-5-PD; First et al., 2015, 2016) by a trained psychiatrist (MS). Inclusion criteria for patients with major depression were: (1) age 18–50 years; (2) a diagnosis of major depression in a current major depressive episode (≥8 points on the Hamilton Depression Rating Scale, 21-item version (Hamilton, 1967).

Exclusion of psychiatric comorbidities, where altered brain activations during the facial emotion recognition tasks have been demonstrated: Considering the available brain imaging data, patients with comorbid borderline personality disorder and PTSD were also excluded, because they have increased sensitivity to negative environmental stimuli, which is associated with increased activation of the amygdala (New et al., 2007; Shin et al., 2005). In our sample, non-excluded psychiatric comorbidities were: anxiety disorders (panic disorder N = 4; social phobia N = 3; generalized anxiety disorder N = 3; specific phobias N = 4); obsessive-compulsive disorder in the past 6 years, and never treated when symptomatic before (N = 2); mild and non-chronic alcohol use disorder (N = 3); lifetime sedatives, hypnotics, and anxiolytics use disorder (N = 3) in full remission for more than 2 years; cluster C personality disorders (dependent N = 3, avoidant N = 2). The mean age of disease onset was 26.11 ± 9.41 years. The mean duration of illness was 6.86 ± 7.46 years (range 0.4–26 years). Thirty-nine (95%) patients with MDD received antidepressant medication (selective serotonin reuptake inhibitor: 25; serotonin and noradrenaline reuptake inhibitor: 3; noradrenergic and specific serotonergic antidepressant: 9; bupropion: 1, agomelatine: 4, trazodone: 2; combined with mood stabilizer: 3; augmented by low-dose atypical antipsychotics: 6).

Based on the severity of childhood maltreatment, depressed patients were divided into two study groups, one with a low incidence of childhood maltreatment (MDD group, N = 19), another one with a history of severe maltreatment (MDD + CM group, N = 21). (For methods used for the assessment of childhood maltreatment please see section 2.2. "Clinical status and childhood trauma assessment" and the Supplementary Materials.)

The healthy control group (N = 21) was matched in age, sex, and level of education to the entire MDD group. Control subjects were screened by a qualified psychiatrist (MS) to ascertain the absence of lifetime or family history of mental disorders; besides, Symptom-Checklist-90-R (Derogatis, 1994; Unoka et al., 2004) was applied to rule out subthreshold psychiatric symptoms. None of the healthy individuals took psychotropic medication. Only healthy control participants with no significant history of childhood maltreatment were enrolled in the study. By using cut-off values on each subscale of the Childhood Trauma Questionnaire, we enrolled only those control subjects who did not score higher than the 'low' range in any trauma dimension (for the exact cut-off values used in this study, please see the Supplementary Materials). After group assignment, MDD + CM patients had significantly lower median of years of education compared to MDD and control subjects. However, there was no significant difference in general IQ between the three study groups. Hence, all three groups were matched in IQ. All participants were Caucasian, native Hungarian speakers living in the urban and suburban area of Pécs and provided written informed consent.

The local Research Ethics Committee of the University of Pécs approved the study design and protocol (Ethical Approval Nr.: 2015/5626).

2.2. Clinical status and childhood trauma assessment

Depression severity was evaluated by a multimethod approach: with the 21-item Hamilton Depression Rating Scale, and with the Beck Depression Inventory (Beck et al., 1961). Anxiety severity was assessed with the Beck Anxiety Inventory (Beck et al., 1988.) The overall level of IQ was estimated with a four-subtest version of the Hungarian adaptation of the Wechsler Adult Intelligence Scale-Revised (Kaufman et al., 1991, Wechsler, 1997; Nagybányai Nagy and Rózsa, 2006).

Childhood maltreatment was defined as exposure to long-lasting and/or repeated abuse and/or neglect before the age of 18. Childhood abuse and neglect were surveyed with a self-report questionnaire: the Hungarian version of the 28-item Childhood Trauma Questionnaire-Short Form (CTQ, Bernstein, et al., 2003; Csernela et al., 2021). CTQ is a widely used, 28-item, retrospective self-report questionnaire designed to assess the severity of five types of childhood maltreatment. CTQ total score and scores for the 5 subscales (physical abuse and neglect, emotional abuse and neglect, as well as sexual abuse) of the CTQ were calculated. By using cut-off values on each subscale, depressed patients scoring in any trauma dimension at least above the 'low' range were assigned to the MDD + CM group. For further details of the assessment of childhood maltreatment, including the CTQ cut-off scores, please see the Supplementary Materials.

Demographic, IQ, clinical, and CTQ data of the sample are presented in Tables 1 and 2.

2.3. The facial emotion recognition paradigm

The facial emotion recognition task is a well-established task that has been employed in numerous neuroimaging studies to characterize the activity of the amygdala and related cortico-limbic structures. Here, we used a modified version of the original facial emotion recognition task (Hariri et al., 2002) using fearful (F), angry (A), and sad (S) images from the FACES database (Ebner et al., 2010).

Our block design facial emotion recognition fMRI paradigm included six blocks of facial emotion processing (face matching) tasks alternating with six blocks of sensorimotor (shape matching) control tasks (C) (Fig. 1). One-half of the trials required left-handed, while the other half required right-handed responses. One block lasted 30sec and contained 6 sequential matching trials. Each trial was presented for 5sec, with no interstimulus interval. The entire paradigm included a total of 12 blocks and 72 trials (6 trials per block; 6 face matching, and 6 shape matching blocks) and lasted for 360sec (e.g., CFCACSCFCACS, see Fig. 1A). Before scanning, subjects underwent detailed instructions about the facial emotion recognition fMRI task, followed by a short training session inside the scanner including both the face matching and the shape matching tasks.

Table 1
Demographic, IQ, and clinical data of the sample.

	Control N = 21	MDD N = 19	MDD + CM N = 21	Between-group differences
Age (yrs)[a]	33.24 ± 8.37 (21–48)	33.21 ± 7.55 (21–50)	32.52 ± 9.55 (18–54)	$F_{(2,58)} = 0.46$, p = 0.955†
No. of females (%)	14 (66.67%)	12 (63.16%)	14 (66.67%)	$\chi2_{(2)} = 0.07$; p = 1.000#
Years of education[b]	15 (12–17)	12 (12–17)	12 (11–15)	$\chi2_{(2)} = 7.753$, p = 0.021¥; post hoc Dunn-Bonferroni: MDD + CM vs HC p < 0.05 MDD + CM vs MDD p < 0.05 MDD vs HC p = 0.63
IQ[c]	112.1 ± 6.58	114.74 ± 4.71	110.95 ± 5.79	$F_{(2,58)} = 0.213$, p = 0.809†
Beck Depression Inventory[c]	4.29 ± 2.92	21.53 ± 3.26	23.10 ± 5.66	$F_{(2,58)} = 130.655$, p < 0.001†; Games-Howell post hoc: MDD + CM vs HC p < 0.001, MDD vs HC p < 0.001, MDD vs MDD + CM p = 0.529
Beck Anxiety Inventory[b]	3 (0.5–10.5)	18 (8–24)	21 (16–33)	$\chi2_{(2)} = 30.916$; p < 0.001¥; post hoc Dunn-Bonferroni: MDD + CM vs HC p < 0.001, MDD vs HC p < 0.001, MDD vs MDD + CM p = 0.453
Age at illness onset (yrs)[b]	–	29 (18–34)	21 (16.5–32.5)	U = 153.0, p = 0.207§
Length of illness (yrs)[b]	–	4 (1–7)	7 (0.4–12.5)	U = 179.0, p = 0.578§
Number of MDD episodes[b]	–	2 (1–2)	2 (1–3)	U = 166.0, p = 0.332§
Antidepressant medication (No/Yes)	–	1/18	0/21	$\chi2_{(1)} = 1.134$, p = 0.4758*
Psychiatric co-morbidities (Yes/No)				
panic disorder	–	1/18	3/18	$\chi2_{(1)} = 0.902$, p = 0.3422*
social anxiety disorder	–	2/17	2/19	$\chi2_{(1)} = 0.011$, p = 0.9159*
specific phobia	–	2/17	2/19	$\chi2_{(1)} = 0.011$, p = 0.9159*
generalized anxiety	–	1/18	2/19	$\chi2_{(1)} = 0.261$, p = 0.6094*
OCD in remission	–	1/18	1/20	$\chi2_{(1)} = 0.005$, p = 0.9421*
AUD in remission	–	1/18	2/19	$\chi2_{(1)} = 0.261$, p = 0.6094*
SHAUD in remission	–	2/17	1/20	$\chi2_{(1)} = 0.478$, p = 0.4894*
dependent PD	–	2/17	1/20	$\chi2_{(1)} = 0.478$, p = 0.4894*
avoidant PD	–	0/19	1/20	$\chi2_{(1)} = 0.928$, p = 0.3354*

† One-way ANOVA; # Chi-square test; ¥ Kruskal-Wallis H test; § Mann-Whitney *U* test; * Fisher's exact test; [a] mean ± SD (range); [b] median (interquartile range); [c] mean ± SD.

Abbreviations: AUD: alcohol use disorder, HC: healthy control; IQ: intelligence quotient; MDD: major depressive disorder; MDD + CM: major depressive disorder with childhood maltreatment. OCD: obsessive-compulsive disorder, PD: personality disorder, SHAUD: sedatives, hypnotics and anxiolytics use disorder.

2.3.1. Emotional face matching task

In the emotional face matching task, we used images only with negative facial expressions. Each face matching block (F, A, and S) was repeated twice with images of different people, balanced for gender in a pseudorandomized order. A target face (on the top of the display) and two test faces (bottom left and right) were presented in a triangular arrangement using Presentation software (Neurobehavioral System, Inc, Berkley, CA, USA). Prior to the examination, subjects were instructed to choose one of the two test faces on the bottom that displayed the same facial emotion as the target face on the top of the screen. The other, incongruent test face was always displaying a neutral facial expression. The face photographs from the FACES database (Ebner et al., 2010) depicted young people (mean age = 24.2, standard deviation = 3.4, age range = 19–31 years) wearing identical standard grey T-shirts without jewelry, glasses, make-up, or other eye-catching items (Fig. 1B).

All stimuli were presented via MRI-compatible goggles (VisualSystem NordicNeuroLab AS, Bergen, Norway) specifically designed for fMRI studies. Subjects made responses by MR-compatible response buttons (ResponseGrip, NordicNeuroLab AS, Bergen, Norway) pressing their left or right thumb fingers depending upon the choice. The decision was marked by a yellow square on the screen, and changes were not possible (Fig. 1A). The presentation of visual stimuli and the recording of subject's responses were implemented in Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA, USA). Reaction time and matching accuracy were obtained offline for each subject from the log files generated during the fMRI measurement. Mean reaction time (ms) and matching accuracy (% of accurate matches) were calculated separately for the shape- and face matching tasks as well as for each subtype of the face matching task (i.e. fearful, angry, and sad faces). Between-group differences in reaction time and matching accuracy data were assessed by Kruskal-Wallis H test followed with Dunn-Bonferroni pairwise post hoc comparisons.

2.3.2. Shape matching task

The shape matching task was used here as a control task, where non-emotional stimuli, i.e. geometric forms are presented to the subjects. We used geometric shapes instead of neutral faces because they may provide a more truly neutral baseline for comparison, particularly when patients are involved (Filkowski and Haas, 2017). During the shape matching task, participants completed trials involving abstract geometric forms (circles, vertical and horizontal ellipses) in an analogous configuration as the face matching task. Subjects were asked to choose one of the two test forms on the bottom that has the same geometric form as the target on the top of the screen. Similarly, a yellow square on the screen marked the participant's decision (see Fig. 1A). During all trials, response accuracy and reaction times for the stimuli were recorded and analyzed as described in 2.3.1.

2.4. Magnetic resonance imaging

All measurements were carried out using a 3T Magnetom TIM Trio whole-body MRI scanner (Siemens AG, Erlangen, Germany) with a 12-channel head coil. Functional imaging was acquired using a 2D single-shot echo-planar imaging sequence (TR/TE = 2500/30 ms; Flip angle = 76°; 36 axial slices with a thickness of 3 mm; FOV = 192 × 192 mm^2; matrix size = 64 × 64; receiver bandwidth = 2170 Hz/pixel; no gap; interleaved slice order to avoid crosstalk between contiguous slices). For distortion correction purposes, field mapping sequence (TR/TE1/TE2 = 402/5.20/7.66 ms; Flip angle = 60°; 36 axial slices; FOV = 228 × 228 mm^2; matrix size = 76 × 76; receiver bandwidth = 259 Hz/pixel) with the same voxel size, orientation and adjustment parameters as the fMRI scan was acquired right after the fMRI measurement. Anatomical images were obtained using an isotropic T1-weighted 3D-MPRAGE sequence (TR/TI/TE: 2530/1100/3.37 ms; Flip angle = 7°; 176 sagittal slices with a thickness of 1 mm; FOV = 256 × 256 mm^2; matrix size = 256 × 256; receiver bandwidth = 200 Hz/pixel).

2.5. fMRI data analysis

For the detailed description of the preprocessing, noise classification

Table 2
Childhood trauma questionnaire data.

	Control N = 21	MDD N = 19	MDD + CM N = 21	Between-group differences
CTQ sum[a]	28 (26.5–33)	34 (31–38)	59 (52.5–70)	$\chi2_{(2)} = 43.323$; $p < 0.001$¥; post hoc Dunn-Bonferroni: MDD + CM vs HC $p < 0.001$, MDD vs HC $p = 0.304$, MDD vs MDD + CM $p < 0.001$
CTQ physical abuse[a]	5 (5–5)	5 (5–5)	9 (6.5–12)	$\chi2_{(2)} = 28.952$; $p < 0.001$¥; post hoc Dunn-Bonferroni: MDD + CM vs HC $p < 0.001$, MDD vs HC $p = 1.000$, MDD vs MDD + CM $p < 0.001$
CTQ physical neglect[a]	5 (5–5)	5 (5–5)	10 (3–13)	$\chi2_{(2)} = 38.636$; $p < 0.001$¥; post hoc Dunn-Bonferroni: MDD + CM vs HC $p < 0.001$, MDD vs HC $p = 0.550$, MDD vs MDD + CM $p < 0.001$
CTQ emotional abuse[a]	6 (5–8)	7 (5–8)	18 (11.5–20)	$\chi2_{(2)} = 36.165$; $p < 0.001$¥; post hoc Dunn-Bonferroni: MDD + CM vs HC $p < 0.001$, MDD vs HC $p = 1.000$, MDD vs MDD + CM $p < 0.001$
CTQ emotional neglect[a]	8 (6–10.5)	11 (8–14)	17 (15–19.5)	$\chi2_{(2)} = 39.747$; $p < 0.001$¥; post hoc Dunn-Bonferroni: MDD + CM vs HC $p < 0.001$, MDD vs HC $p = 0.133$, MDD vs MDD + CM $p < 0.001$
CTQ sexual abuse[a]	5 (5–5)	5 (5–5)	5 (5–9.5)	$U = 128.0$, $p = 0.014$§
Percent of subjects reporting maltreatment	**Control N = 21**	**MDD N = 19**	**MDD + CM N = 21**	
Physical abuse				
none:	95.2%	100%	38.1%	
low:	4.8%	–	23.8%	
moderate:	–	–	28.6%	
severe:	–	–	4.8%	
Physical neglect				
none:	100%	90.5%	14.3%	
low:	–	9.5%	28.6%	
moderate:	–	–	33.3%	
severe:	–	–	23.8%	
Emotional abuse				
none:	85.7%	78.9%	4.8%	
low:	14.3%	21.1%	28.6%	
moderate:	–	–	9.5%	
severe:	–	–	57.1%	
Emotional neglect				
none:	57.1%	42.1%	–	
low to moderate:	42.9%	57.9%	4.8%	
moderate:	–	–	52.4%	
severe:	–	–	42.8%	
Sexual abuse:				
none:	100%	94.7%	57.1%	
low:	–	5.3%	14.3%	
moderate:	–	–	23.8%	
severe:	–	–	4.8%	

¥ Kruskal-Wallis H test; Abbreviations: CTQ: Childhood Trauma questionnaire. HC: healthy control; MDD: major depressive disorder; MDD + CM: major depressive disorder with childhood maltreatment.
[a] median (interquartile range)

and clean-up please see the Supplementary Materials. After these steps, whole-brain general linear model (GLM) time-series statistical analyses of the individual data sets were carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction.

To examine the association of severe to extreme childhood maltreatment a higher-level mixed-effects analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects, stage 1 and 2) with outlier de-weighting in the following order:

i. Within-group activations: activation pattern during the facial emotion matching task in the control, MDD, and MDD + CM groups separately (face matching task > shape matching task contrasts, or positive BOLD responses);
ii. Within group-deactivations: deactivation pattern during the facial emotion matching task in the control, MDD, and MDD + CM groups separately (shape matching task > face matching task contrasts, or negative BOLD responses);
iii. Between-group differences of activation patterns during the facial emotion matching task controlled for age and gender (pairwise group comparisons were performed, if the omnibus F-test was significant);
iv. Between-group differences of deactivation patterns during the facial emotion matching task controlled for age and gender (pairwise group comparisons were performed if the omnibus F-test was significant);
v. Clinical data (and CTQ scores) × group interaction effect on the BOLD response during the facial emotion matching task.

For steps iii., iv., and v. (i.e. in between-group comparisons, as well as when estimating variable × group interaction effects) a voxel-wise F-test was applied to detect any significant general effect. If the F-test yielded a significant effect, then further pairwise t-tests (for steps iii. and iv.) and correlations (for step v.) were used to determine the direction of the difference. Voxels overlaid with the F-test were interpreted only for

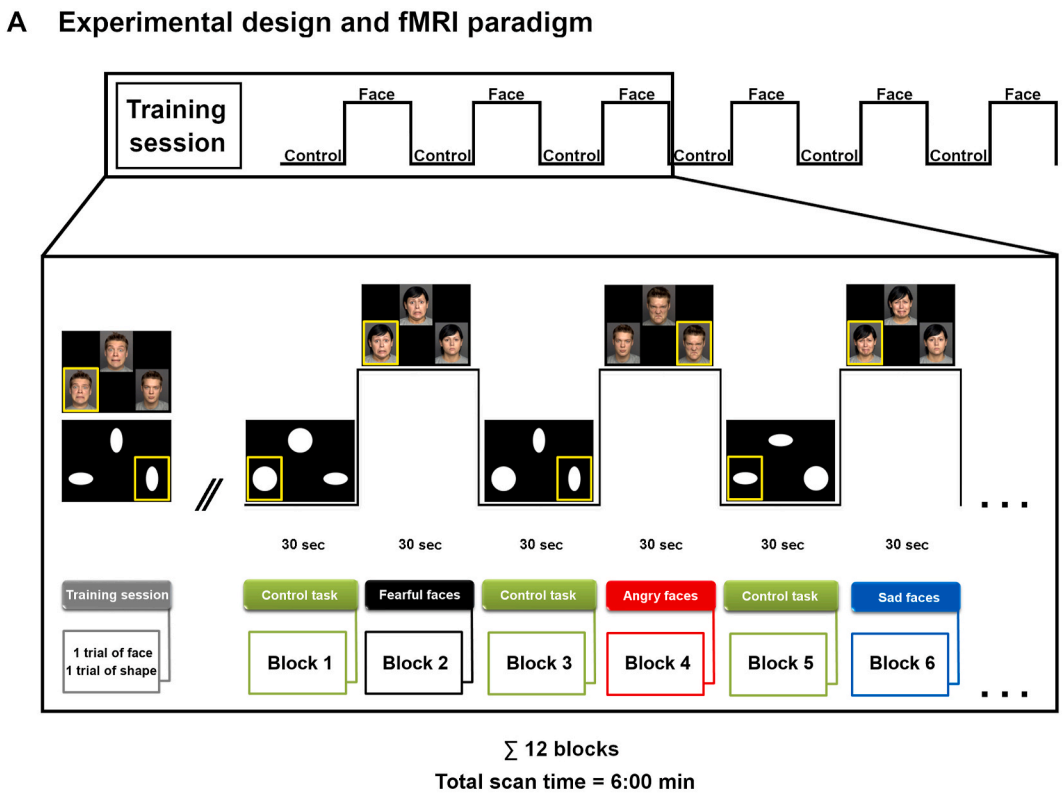

Fig. 1. Experimental design of our facial emotion recognition task with examples of images with emotional stimuli. **A**: After a short training session (1 trial of face and 1 trial of shape), the block design task included 6 blocks of a 30-s-long shape matching task (control) alternating with a 30-s-long face matching task (face). The face matching task contained a total of 2 fearful, 2 angry, and 2 sad faces blocks interleaved with control (shape matching) tasks. One block contained 6 sequential matching trials, each was presented for 5s with no interstimulus interval. The whole run contained a total of 12 blocks and 72 trials (6 face match and 6 shape match blocks) and it lasted for 360 s without the training session. Subjects were instructed to match one of the two test shapes or faces on the bottom that were similar (in shape) or expressed the same emotion as the target shape/face on the top of the screen. **B**: Representative images of faces with various emotional expressions. Each match emotion trial included a trio of male or female faces expressing neutral, fearful, angry, and sad emotions.

each separate *t*-test. Family-wise error (FWE) correction was used to control for multiple comparisons. Statistical maps were considered to be significant at $Z > 2.3$ and an FWE corrected cluster significance threshold of $p = 0.05$ (Worsley, 2001). Brain regions with significant BOLD responses were located using the Harvard Oxford cortical and subcortical structural atlas, part of FSL 5.0.7 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

2.6. Statistical analysis of demographic, clinical, and behavioral data

Data analysis was performed using an SPSS statistical software package (Version 23.0, IBM Corp.). Nonparametric data and datasets with skewed distributions were compared with the Mann-Whitney *U* test, as well as with the Kruskal-Wallis H test followed with Dunn-Bonferroni pairwise post hoc comparison. The level of significance was set at $p < 0.05$.

3. Results

No significant differences were observed between the three groups for age, sex, and IQ. MDD + CM patients had significantly fewer years of education compared to MDD patients and control subjects (Table 1). Clinical variables of the two clinical groups with major depression did not significantly differ (Table 1). Due to the group assignment criteria, MDD + CM patients' CTQ scores differed significantly from those of both the control and MDD groups on each subscale (Table 1). There was no significant between-group difference in CTQ scores of MDD patients (without a history of childhood maltreatment) and controls.

3.1. Reaction time and matching accuracy during the facial emotion matching task

3.1.1. Matching accuracy of facial emotions

Participants had a high overall response accuracy. There was no significant between-group difference in the shape-matching accuracy. However, study groups significantly differed in matching facial emotions ($\chi^2(2) = 6.019$; $p = 0.049$), the MDD + CM group performed significantly worse compared to HC (posthoc Dunn-Bonferroni pairwise comparison, $p = 0.037$, mean rank scores: MDD + CM = 24.81, HC = 36.31, $p = 0.045$). Moreover, we found a significant between-group difference in the matching accuracy of sad faces ($\chi^2(2) = 6.286$; $p = 0.043$, Table 3). MDD + CM patients were significantly less accurate in matching sad faces than the healthy controls (posthoc Dunn-Bonferroni pairwise comparison, $p = 0.037$, mean ranks sores: HC = 36.50, MDD = 31.18, MDD + CM = 25.33). There was no between-group difference in the accuracy of matching fearful and angry faces.

3.1.2. Reaction time

There was a significant between-group difference in the reaction times in response to sad faces ($\chi^2(2) = 7.054$; $p = 0.029$). MDD patients reacted significantly slower compared to controls (posthoc Dunn-Bonferroni pairwise comparison, $p = 0.024$, mean rank scores: HC = 24.14, MDD = 39.05, and MDD + CM = 30.57). No other statistically significant between-group difference was found in the reaction times.

All matching accuracy and reaction time data are presented in Table 3.

3.2. Functional MRI

3.2.1. Within-group BOLD responses

3.2.1.1. Groupwise activation patterns. We found significant activation in typical visual-limbic and prefrontal regions involved in emotion, and face processing, as well as recognition, including the occipital face area, the amygdala, the hippocampus, the middle and the inferior frontal gyri in all three groups (Tables 4 and 5; Figs. 2A, 3A and 4A). Other regions like the occipital pole, the thalamus, the posterior paracingulate gyrus, the lingual gyrus, the intra- and the supracalcarine cortices, the precentral gyrus, the posterior division of the superior temporal gyrus, the posterior supramarginal gyrus, the medial frontal cortex, and the insular cortex were also activated (Figs. 2A, 3A and 4A).

3.2.1.2. Groupwise deactivation patterns. Control subjects exhibited significant deactivation in regions responsible for processing reward, fearful stimuli, and emotional regulation: i.e. n. accumbens, subcallosal cortex, anterior and posterior cingulate gyrus (Table 4, Fig. 2B), but no significant deactivation pattern was found in the n. accumbens of MDD patients (Table 5, Fig. 3B) and the n. accumbens and subcallosal cortex

Table 4
BOLD responses during the facial emotion matching task in the control group.

Cluster	No. of voxels	Areas	Z-score	x	y	z
Activation pattern (face matching > shape matching contrast)						
1	38057	left occipital face area	5.69	−46	−79	−12
		right occipital face area	6.47	46	−76	−6
		left amygdala	5.42	−22	−6	−16
		right amygdala	5.28	18	−4	−18
		left middle frontal gyrus	4.83	−48	28	28
		left inferior frontal gyrus	5.48	−46	12	28
		left hippocampus	4.52	−24	−28	−10
		right hippocampus	4.72	24	−30	−6
2	5851	right middle frontal gyrus	5.39	50	30	24
		right inferior frontal gyrus	6.02	46	16	24
Deactivation pattern (shape matching > face matching contrast)						
1	2386	left accumbens	3.93	−12	10	−10
		right accumbens	3.23	6	10	−6
		subcallosal cortex	4.84	−2	28	−10
		anterior cingulate gyrus	3.19	−6	38	−2
2	2051	posterior cingulate gyrus	4.38	2	−24	38

Statistical maps were considered to be significant at Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05.
Z-score: Z-scores of local maxima; x-, y- and z values correspond to the MNI coordinates of local maxima in mm; several local maxima are reported if the cluster encompasses more than one anatomical location. BOLD: blood-oxygen-level-dependent.

Table 3
Reaction time and response accuracy in the facial emotion matching task: between-group comparisons.

	Groups*			Between-group comparisons**			
	HC	**MDD**	**MDD + CM**	Kruskal-Wallis H test	HC *vs.* MDD	HC *vs.* MDD + CM	MDD + CM *vs.*MDD
Reaction time (ms)							
Shape matching tasks	1011.87 ± 250.43	1103.38 ± 324.73	1104.71 ± 282.16	ns	–	–	–
Face matching tasks	1567.87 ± 368.41	1841.40 ± 376.23	1749.38 ± 496.70	ns	–	–	–
fearful faces	1522.17 ± 366.11	1738.75 ± 386.30	1641.37 ± 448.65	ns	–	–	–
angry faces	1505.00 ± 379.38	1724.95 ± 390.43	1765.66 ± 588.86	ns	–	–	–
sad faces	1676.44 ± 425.37	2060.49 ± 459.13	1841.13 ± 521.83	0.029	0.024	ns	ns
Matching accuracy (% of correct responses)							
Shape matching tasks	98.67 ± 1.67	98.68 ± 1.70	97.62 ± 3.86	ns	–	–	–
Face matching tasks	99.34 ± 1.21	98.68 ± 1.94	96.83 ± 3.76	0.049	ns	0.045	ns
fearful faces	99.60 ± 1.82	99.12 ± 2.63	97.62 ± 4.67	ns	–	–	–
angry faces	99.60 ± 1.82	100.00 ± 0.00	99.60 ± 1.82	ns	–	–	–
sad faces	98.81 ± 2.99	96.93 ± 4.98	93.65 ± 8.70	0.043	ns	0.037	ns

*Data are presented as mean ± standard deviation.
HC: healthy control, MDD: major depressive disorder (without childhood maltreatment); MDD + CM: major depressive disorder with childhood maltreatment.
**Assessed by Kruskal-Wallis H and Dunn–Bonferroni posthoc pairwise comparison tests. In case of statistically significant results, p-values are presented. ns: not significant.

Table 5
BOLD responses during the facial emotion matching task in the MDD group.

Cluster	No. of voxels	Areas		Z-score	x	y	z
Activation pattern (face matching > shape matching contrast)							
1	38471	left occipital face area		5.14	−38	−80	−12
		right occipital face area		5.98	40	−82	−10
		left amygdala		4.98	−24	−2	−18
		right amygdala		4.71	20	−4	−14
		left middle frontal gyrus		4.00	−50	24	28
		right middle frontal gyrus		5.66	48	30	24
		left inferior frontal gyrus		4.40	−54	18	23
		right inferior frontal gyrus		5.75	48	14	22
		left hippocampus		4.43	−22	−32	−6
		right hippocampus		4.05	22	−32	−6
Deactivation pattern (shape matching > face matching contrast)							
1	2472	subcallosal cortex	3.93		2	28	−8
		anterior cingulate gyrus	4.24		2	36	−2
2	2316	posterior cingulate gyrus	5.27		2	−24	42

Statistical maps were considered to be significant at Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05.
Z-score: Z-scores of local maxima; x-, y- and z-values correspond to the MNI coordinates of local maxima in mm; several local maxima are reported if the cluster encompasses more than one anatomical location. BOLD: blood-oxygen-level-dependent; MDD: major depressive disorder.

of the MDD + CM group (Table 6, Fig. 4B). In the MDD + CM group, additional significant deactivation was found in the pre-, and postcentral gyri (Table 6, Fig. 4B). Other regions like the anterior paracingulate gyrus, the planum temporale, the parietal operculum cortex, the anterior supramarginal gyrus, the angular gyrus, and the precuneus cortex were also deactivated in all three groups (Figs. 2B, 3B and 4B).

3.2.2. Between-group differences in BOLD responses

There was no statistically significant between-group difference in activation patterns during the facial emotion matching tasks. However, after controlling for age and gender, significant differences in negative BOLD response were found between the control, MDD, and MDD + CM groups in the right accumbens, the subcallosal cortex, the anterior paracingulate gyrus, the right pre- and postcentral gyri (Fig. 5).

Pairwise *t*-tests revealed that control subjects had significantly increased negative BOLD response during the facial emotion matching tasks in the right accumbens, the subcallosal cortex, and the anterior paracingulate gyrus compared to the MDD + CM group. Also, the pairwise between-group comparison confirmed significantly increased negative BOLD response in the anterior paracingulate gyrus of MDD patients compared to MDD + CM patients. The right precentral and postcentral gyrus were characterized by a significantly increased negative BOLD response in patients with MDD + CM compared to the control group (Table 7).

3.2.3. Interaction effect between clinical data and groups on the BOLD response

There was a significant interaction effect between clinical data and MDD *versus* MDD + CM groups on the BOLD response (in face matching *versus* shape matching contrasts) in respect to the number of depressive episodes and age at illness onset. Significant group × number of depressive episodes interaction was found in the anterior cingulate and posterior paracingulate gyri. Further analysis showed a positive correlation of BOLD response and the number of depressive episodes in the anterior cingulate and posterior paracingulate gyri of MDD + CM patients (Table 8, Fig. 6A), while there was no significant correlation in the MDD group. Significant group × age at illness onset interaction was found in the posterior division of the left superior and the middle temporal gyri with a significant positive correlation between BOLD signal and age at illness onset in the MDD group (see Table 8 and Fig. 6B), but no significant correlation was found in MDD + CM patients.

There was no other significant group × clinical variable interaction including depression (Beck Depression Inventory), and anxiety (Beck Anxiety Inventory) scores, as well as CTQ scores.

4. Discussion

To our best of knowledge, our present fMRI study is the first in the literature to investigate brain activation patterns of control subjects and MDD patients with and without a history of childhood maltreatment using a facial emotion recognition task. Participants of the three experimental groups were matched for age, gender, and IQ. We report here that MDD patients with childhood maltreatment had impaired accuracy in facial emotion recognition in general and that they were significantly less accurate in recognizing sad facial expressions. Several brain areas were activated and deactivated during the facial emotion recognition task, but we could not find any group differences in the activation patterns. Instead, group differences emerged only when we compared the deactivation patterns of the three groups. MDD patients with childhood maltreatment had significantly reduced negative BOLD response in their right accumbens, subcallosal cortex and anterior paracingulate gyrus compared to controls. Furthermore, MDD + CM patients had reduced negative BOLD signals in the anterior paracingulate gyrus compared to the MDD group. Finally, depressed patients with childhood maltreatment had significantly increased negative BOLD signals in their right precentral and postcentral gyri compared to controls. In harmony with our original hypothesis, MDD patients who suffered childhood maltreatment displayed altered emotional processing in a facial emotion recognition task, but we found little difference between the MDD and MDD + CM groups.

4.1. Experience of childhood maltreatment impairs facial emotion recognition

A large body of evidence indicates that the developing brain is particularly vulnerable to stressful childhood experiences. The repeated or sustained hyperactivation of the stress response system during brain development may alter the maturation of core aspects of socio-cognitive functions and often results in disrupted emotion regulation, altered reward processing, and cognitive impairments (Shonkoff et al., 2009; Pechtel and Pizzagalli, 2011; Rokita et al., 2018; Kraaijenvanger et al., 2020). An increasing amount of neuroimaging studies document long-lasting alterations in the activity of limbic circuits which in turn modify the functioning of four key domains: emotion and memory processing, inhibitory control, and reward processing (McCrory et al., 2017; Kraaijenvanger et al., 2020).

In our study, MDD patients who were exposed to childhood maltreatment were impaired in facial emotion recognition, their emotion recognition accuracy was reduced, especially when matching the sad face stimuli. There are a few reports in the literature that

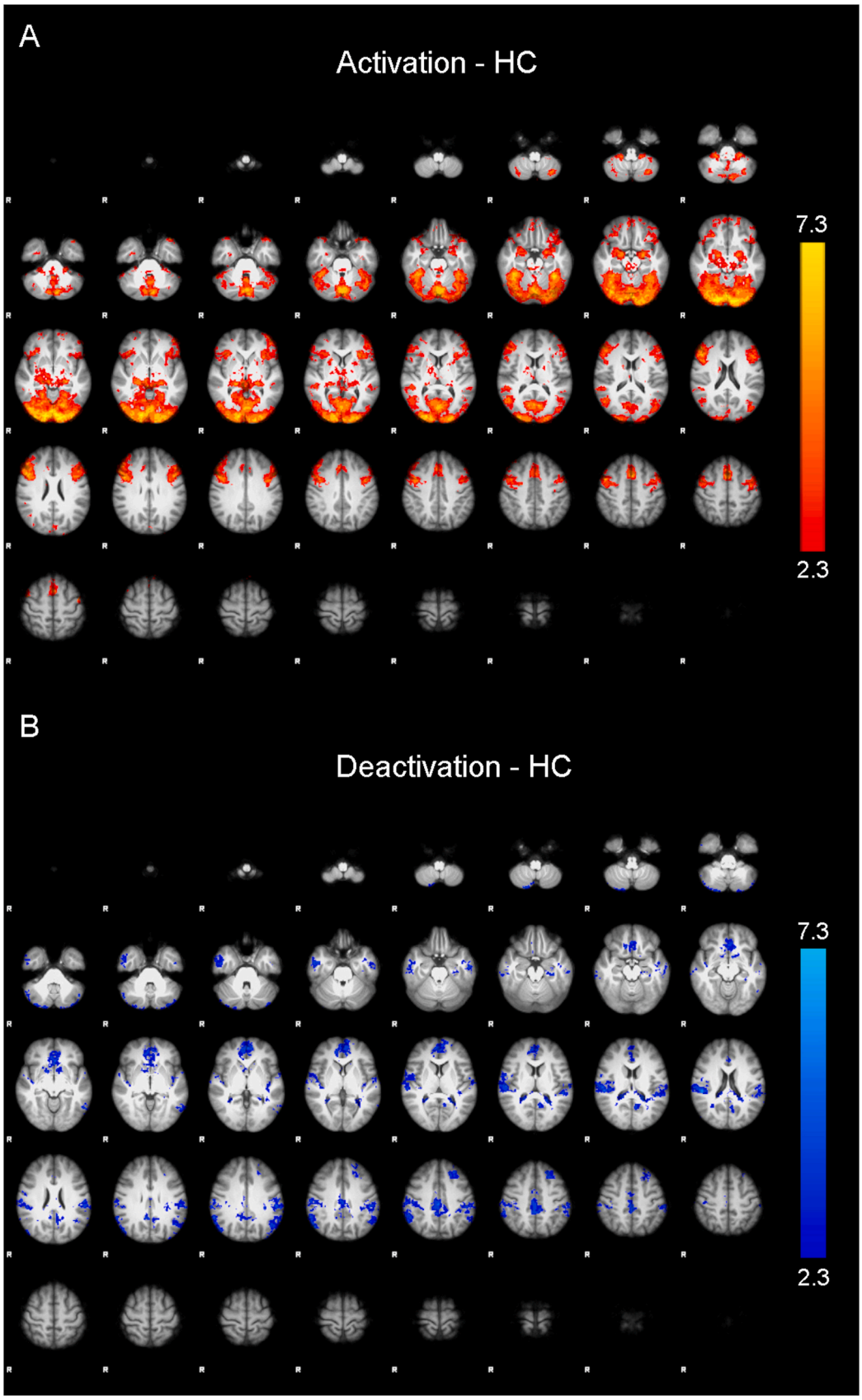

Fig. 2. Group level activations, i.e. face matching > shape matching contrast (**A**) and deactivations, i.e. shape matching > face matching contrast (**B**) during the facial emotion recognition task in healthy controls (HC). Images were thresholded using clusters determined by Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05. Axial slices are shown in radiological convention for MNI slice coordinates from Z = -72 mm to Z = 84 mm.

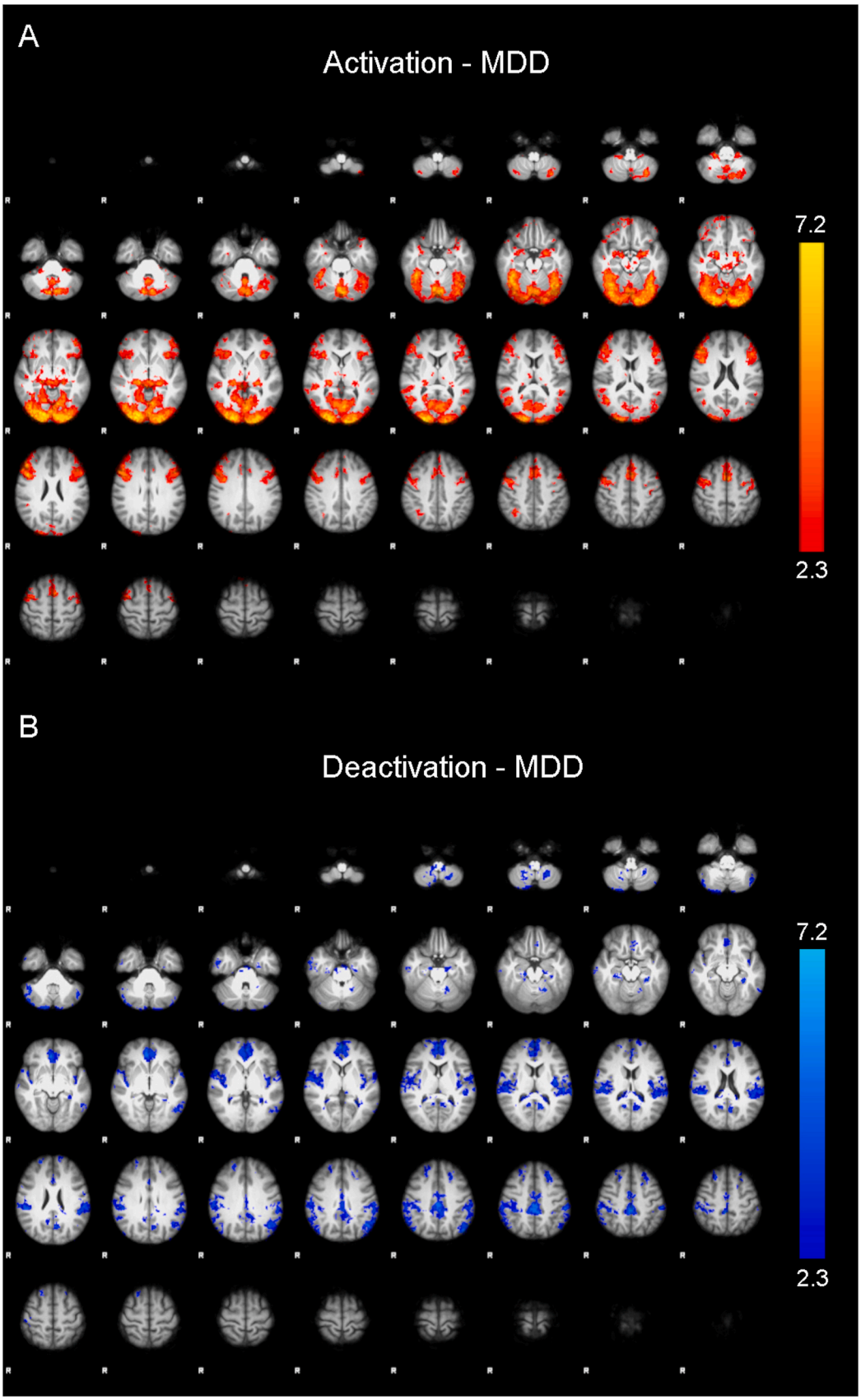

Fig. 3. Group level activations, i.e. face matching > shape matching contrast (**A**) and deactivations, i.e. shape matching > face matching contrast (**B**) during the facial emotion recognition task in MDD patients. Images were thresholded using clusters determined by Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05. Axial slices are shown in radiological convention for MNI slice coordinates from Z = -72 mm to Z = 84 mm.

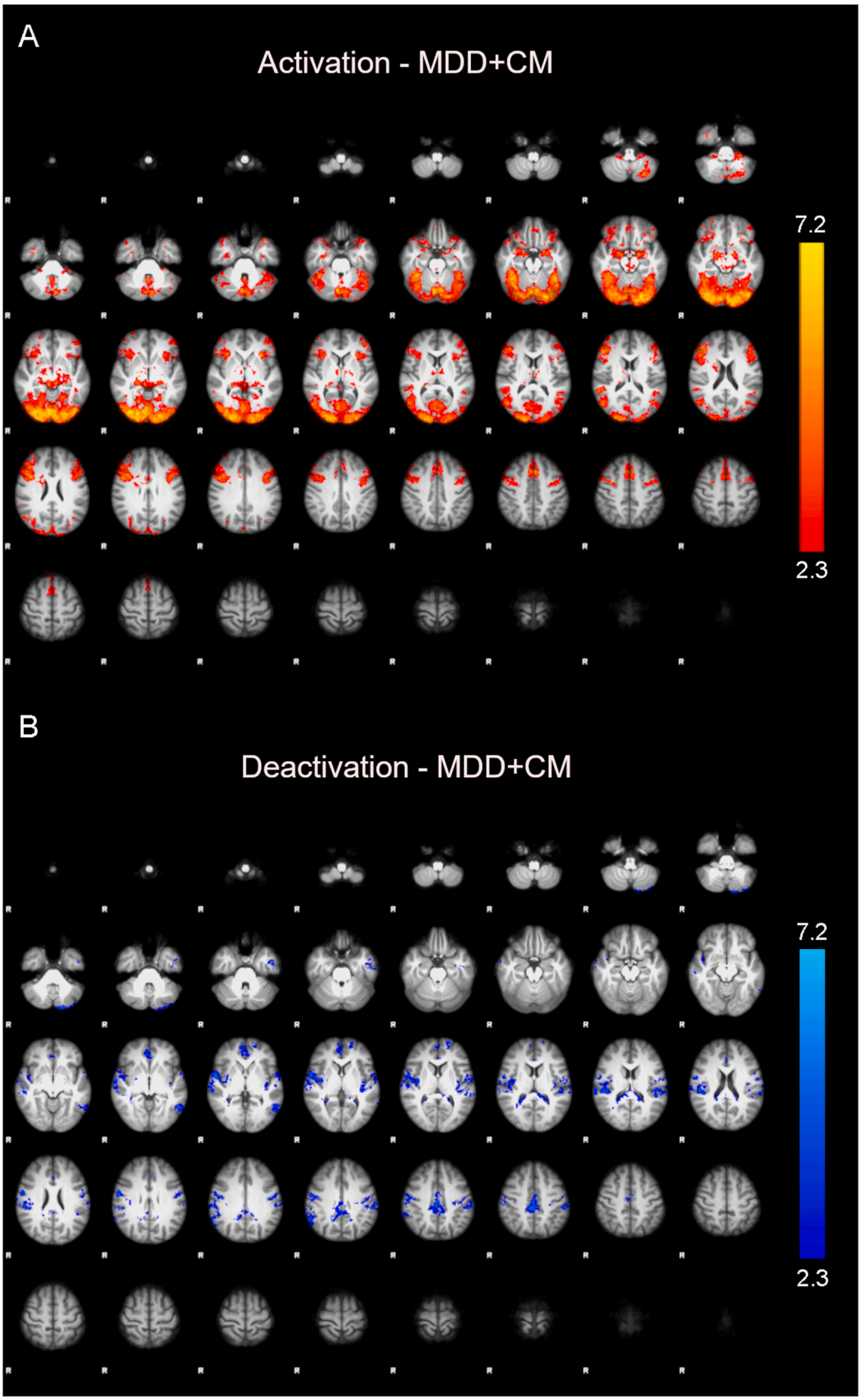

Fig. 4. Group level activations, i.e. face matching > shape matching contrast (**A**) and deactivations, i.e. shape matching > face matching contrast (**B**) during the facial emotion recognition task in MDD + CM patients. Images were thresholded using clusters determined by Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05. Axial slices are shown in radiological convention for MNI slice coordinates from Z = -72 mm to Z = 84 mm.

Table 6
BOLD responses during the facial emotion matching task in the MDD + CM group.

Cluster	No. of voxels	Areas	Z-score	x	y	z
Activation pattern (face matching > shape matching contrast)						
1	25586	left occipital face area	6.47	−42	−82	−12
		right occipital face area	5.93	40	−86	−6
2	14515	left amygdala	5.03	−26	−4	−18
		right amygdala	4.27	20	−4	−16
		left middle frontal gyrus	3.87	−48	28	26
		right middle frontal gyrus	4.07	48	30	24
		left inferior frontal gyrus	4.23	−50	16	26
		right inferior frontal gyrus	4.96	48	16	24
		left hippocampus	3.39	−26	−30	−8
		right hippocampus	3.33	24	−32	−6
Deactivation pattern (shape matching > face matchin contrastg)						
1	3212	right precentral gyrus	3.20	60	2	30
		right postcentral gyrus	3.43	54	−12	44
2	1790	left precentral gyrus	3.15	−58	−2	30
		left postcentral gyrus	2.98	−60	−18	40
3	1043	posterior cingulate gyrus	5.14	6	−32	44
4	500	anterior cingulate gyrus	3.20	0	36	−4

Statistical maps were considered to be significant at Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05.
Z-score: Z-scores of local maxima; x-, y- and z-values correspond to the MNI coordinates of local maxima in mm; several local maxima are reported if the cluster encompasses more than one anatomical location. BOLD: blood-oxygen-level-dependent; MDD + CM: major depressive disorder with childhood maltreatment.

demonstrated that childhood adversity can result in impairment of facial emotion recognition. For example, a study that examined young street children in a forced-choice facial expressions recognition task reported that the maltreated children had impaired recognition accuracy for fear and sad faces and increased accuracy for angry faces (Ardizzi et al., 2015). Another study that investigated abused and non-abused children using the children's version of the Reading the Mind in the Eyes Test found that abused children were significantly impaired in emotion recognition and that their recognition accuracy rates for positive emotion stimuli were significantly lower, but not for negative emotion stimuli (Koizumi and Takagishi, 2014). Using the Reading the Mind in the Eyes Test in adults, we also found that the experience of childhood adversity was associated with an impaired response accuracy in depressed patients and that the number of childhood adversities was a significant predictor of the total Reading the Mind in the Eyes Test scores in MDD (Simon et al., 2019). Furthermore, the impaired recognition accuracy of anger was reported in patients with bipolar disorder who experienced childhood trauma (Russo et al., 2015). Altogether, accumulating evidence suggests that childhood adversity may result in a lasting deficit in facial emotion recognition.

To our best of knowledge, there are hardly any studies which investigated the influence of childhood maltreatment on emotional recognition in depressed patients. A recent study which examined the effect of early life adversity in a heterogeneous (trans-diagnostic) group of patients with internalizing psychopathology included some patients with MDD as well. They found that participants with a combined history of maltreatment and internalizing psychopathology had increased corticolimbic reactivity to fearful facial expressions and greater activation of somatosensory areas during fear and anger processing (Peters et al., 2019). They stated that childhood adversity among patients with internalizing psychopathology "augments the engagement of brain regions involved in emotion processing, above and beyond what is accounted for by current symptoms" (Peters et al., 2019). Another study investigated the influence of childhood maltreatment on attentional biases to sad and happy facial expressions in depressed individuals and reported a positive association between childhood trauma and attentional bias to sad faces (Günther et al., 2015). While more recently, another study examining attentional bias using an eye-tracking method reported that depressed patients showed shorter gaze durations for happy faces, and that childhood maltreatment was associated with

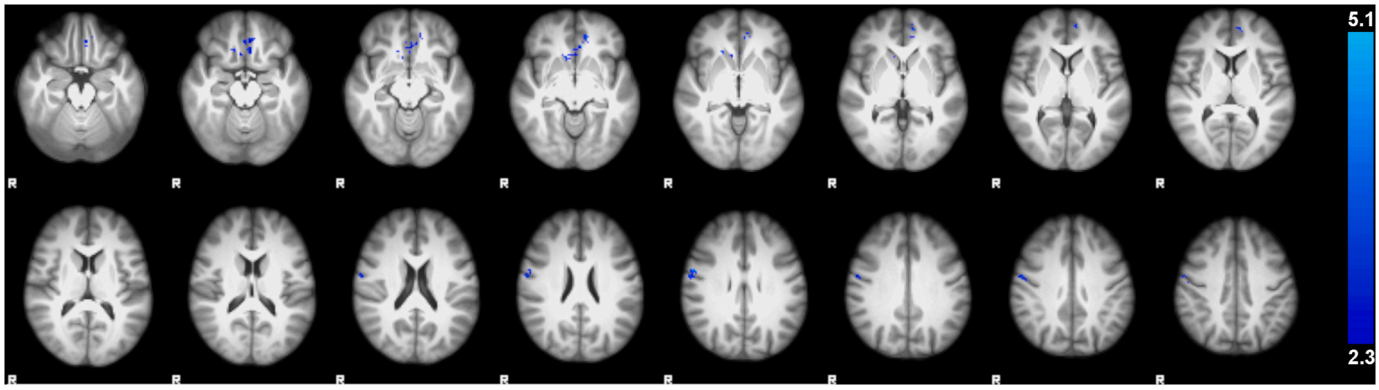

Fig. 5. The significant results of pairwise between-group comparisons of BOLD responses during the facial emotion matching task among the three groups, i.e. Control *versus* MDD, Control *versus* MDD + CM and MDD *versus* MDD + CM. To account for the post-hoc character of these between-group statistical tests and to reduce the chance of false-positive findings, only those voxels are shown as significant, where the omnibus F-test also revealed a significant group effect. Significant differences were found in the negative BOLD response during the facial emotion matching task, i.e. Control > MDD + CM, MDD > MDD + CM and MDD + CM > Control, where ">" means increased negative BOLD signal. Since there were only a few differences, these are presented here in a single figure. More details about these group-differences are presented in Table 7. The images were thresholded using clusters determined by Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05. The presented results are controlled for age and sex and masked with significant F-test results (Z > 2.3, cluster-wise p < 0.05) to avoid false-positive findings. Axial slices are shown in radiological convention for MNI slice coordinates from Z = -20 to 40 mm.

Table 7
Between-group differences in negative BOLD response during the facial emotion matching task.

Contrast	Cluster	No. of voxels	Areas	Z-score	x	y	z
HC > MDD + CM	1	636	right accumbens	3.74	10	18	−6
			subcallosal cortex	3.17	−4	22	−16
			anterior paracingulate gyrus	3.92	−10	50	0
MDD > MDD + CM	1	119	anterior paracingulate gyrus	3.50	−10	52	6
MDD + CM > HC	1	148	right precentral gyrus	3.38	60	2	28
			right postcentral gyrus	4.65	56	−6	36

Statistical maps were considered to be significant at Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05 Between-group differences were controlled for age and gender.
Z-score: Z-scores of local maxima; x-, y- and z-values correspond to the MNI coordinates of local maxima in mm; several local maxima are reported if the cluster encompasses more than one anatomical location. BOLD = blood-oxygen-level-dependent; HC = healthy control; MDD: major depressive disorder; MDD + CM: major depressive disorder with childhood maltreatment.

Table 8
Correlation of clinical data with BOLD response in the MDD + CM and the MDD groups.

Clinical parameter	Group	Cluster	No. of voxels	Areas	Z-score	x	y	z
Number of episodes	MDD + CM	1	220	anterior cingulate gyrus	4.57	6	14	38
				posterior paracingulate gyrus	3.98	6	18	44
Age of illness onset	MDD	1	185	left superior temporal gyrus, posterior division	3.69	−58	−26	−2
				left middle temporal gyrus, posterior division	4.32	−58	−32	−8

Statistical maps were considered to be significant at Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05.
Z-score: Z-scores of local maxima; x-, y- and z-values correspond to the MNI coordinates of local maxima in mm; several local maxima are reported if the cluster encompasses more than one anatomical location. BOLD: blood-oxygen-level-dependent; MDD + CM: major depressive disorder with childhood maltreatment; MDD: major depressive disorder.

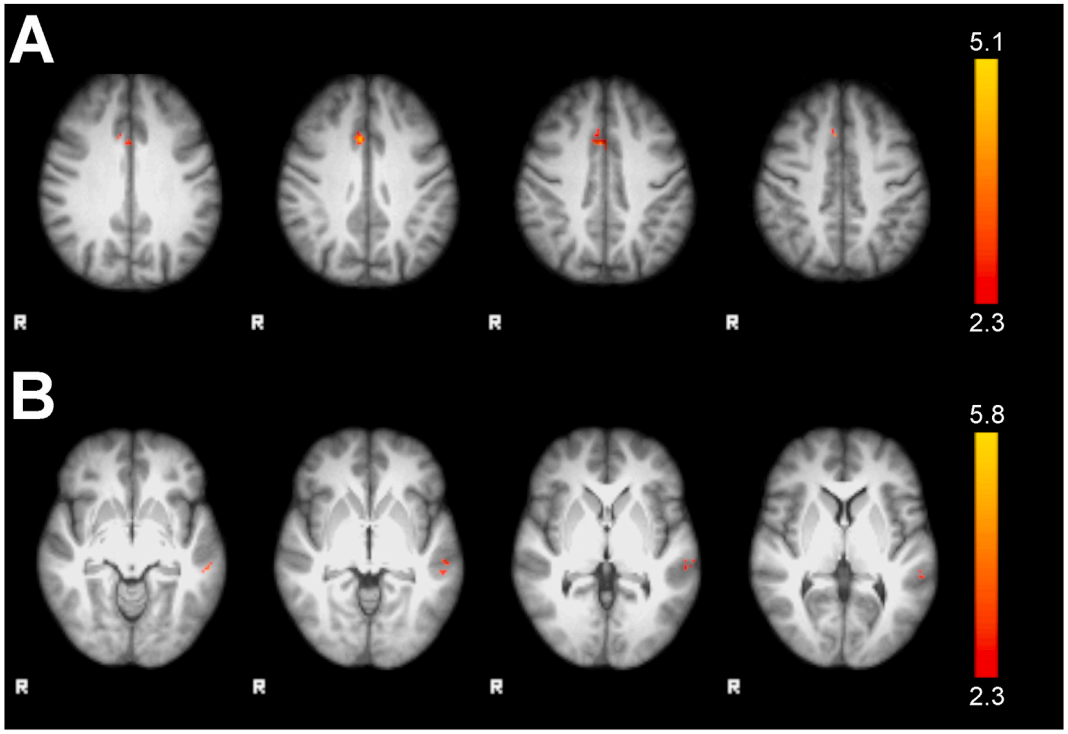

Fig. 6. Group level positive associations between BOLD response and number of depressive episodes in the MDD + CM group (**A**) and between BOLD response and age at illness onset in MDD subjects (**B**) during the facial emotion matching task. Images were thresholded using clusters determined by Z > 2.3 and an FWE corrected cluster significance threshold of p = 0.05. Axial slices are shown in radiological convention for MNI slice coordinates from Z = 32–44 mm (**A**) and Z = -8 to 4 mm (**B**). Significant interaction effects were masked with the results of the F-test to avoid false-positive results.

reduced attention for angry and sad facial expressions, suggesting that maltreated individuals avoid threatening or burdensome stimuli (Bodenschatz et al., 2019).

4.2. Between-group differences in negative BOLD response

In the present study, we found between-group differences only in the negative BOLD response. MDD patients with childhood maltreatment had significantly reduced negative BOLD responses in their right accumbens, subcallosal cortex and anterior paracingulate gyrus and

increased negative BOLD responses in their right precentral and postcentral gyri compared to controls. The nucleus accumbens and the subcallosal cortex are subareas of the reward system (Breiter et al., 1997; Breiter and Rosen, 1999). As a part of the mood regulation network, the subcallosal gyrus (BA 25/32) is of key importance in MDD and has been a target for deep brain stimulation in treatment-resistant depression (Hamani et al., 2011). It is well documented, that the ventromedial medial prefrontal cortex plays a vital role in emotion recognition and emotion experience (Heberlein et al., 2008). Moreover, the medial PFC is involved in mentalizing (or theory of mind) and other higher-order social cognitive functions that require inferring other people's minds (Walter et al., 2004; Gallagher et al., 2000; Amodio and Frith, 2006). The ventral-rostral part of the medial PFC has also been implicated to have a regulatory function on limbic regions involved in producing emotional responses and dampening fear responses (Etkin et al., 2011). Also, as part of the default mode network, cortical midline structures, such as the anterior region of the medial PFC are involved in self-referential thinking (Buckner et al., 2008). Self-focus and self-ruminative patterns of thoughts are key issues in MDD, and functional brain imaging studies have typically found abnormal activation patterns in the ventromedial PFC (Hamani et al., 2011). Similarly, significantly lower deactivation of the ventromedial PFC occurred in MDD + CM patients when they were compared with the MDD group, while there was no difference between the control and MDD groups. Thus, depressed patients' diminished neural response in regions involved in reward processing, mood regulation, mentalizing, and controlling self-referential thinking during the confrontation with faces expressing negative emotions seems to be specific to depressed patients with a history of childhood maltreatment, but not to MDD without maltreatment when compared with healthy controls.

Patients with MDD + CM had significantly higher negative BOLD signals in their right precentral and postcentral gyri. The precentral gyrus is the site of the primary motor cortex which controls voluntary movements, whereas, the postcentral gyrus is the location of the primary somatosensory cortex. The increased negative BOLD signal in the right primary motor and somatosensory cortices of the MDD + CM patients might have also contributed to their impaired performance in the facial emotion recognition task, since they had to respond to the face stimuli with a voluntary finger movement, i.e. pressing with their left (or right) thumb fingers depending on the choice. Furthermore, it has been shown that the right somatosensory cortex is required for the recognition of facial emotion expressions, and damage to this brain area results in emotion recognition deficits (Adolphs et al., 2000). The theory explaining this mechanism is that we recognize another individual's emotional state by using our internal representation of a facial expression maintained in our somatosensory cortex.

In our study, we found between-group differences only in the negative BOLD responses during the facial emotion matching task. Most fMRI studies focus an rely on positive BOLD responses, but negative BOLD responses have also been reported in emotion processing fMRI tasks. Altered negative BOLD responses in the default-mode network have been documented in depressed patients and this decreased negative BOLD response correlated with depression severity and feelings of hopelessness (Grimm et al., 2009). Reduced deactivation in reward circuitry and midline structures have been reported in borderline personality disorder (Enzi et al., 2013), and bipolar patients respond with decreased activation in their frontal cortex and left posterior cortical midline structures (Marchand et al., 2011). The exact cellular mechanisms underlying the negative BOLD responses are not yet clear. The most likely explanation is neural inhibition (Sten et al., 2017), but increased neuronal activity has also been implicated in the generation of negative BOLD signals (Schridde et al., 2008). Notably, an fMRI study using an emotional processing paradigm and resting-state magnetic resonance spectroscopy measurements reported that the negative BOLD responses in the anterior cingulate cortex correlated with gamma-aminobutyric acid (GABA) concentration in the same region (Northoff et al., 2007). To our best of knowledge GABAergic neurotransmission has not been investigated specifically in depressed patients with childhood maltreatment, but there are numerous reports for GABAergic disturbances in depressed patients (Luscher et al., 2011; Duman et al., 2019). Furthermore, animal experiments demonstrate lasting alterations of GABAergic signaling in response to early life stress (Martisova et al., 2012; Albrecht et al., 2017).

Contrary to some previous research findings, we did not find a significant between-group difference in the BOLD response of the amygdala to negative facial emotions. However, amygdala hyperactivation has been found to be one of the core features of the pathophysiology of MDD (Price and Drevets, 2010) and the normalized amygdala has been considered as a key component of symptom remission (Sheline et al., 2001; Fu et al., 2004). Moreover, increased amygdala reactivity to sad face stimuli has been documented repeatedly both in depressed patients (Dannlowski et al., 2007; Peluso et al., 2009; Victor et al., 2010) and in individuals who experienced childhood adversity (Dannlowski et al., 2012, 2013; Hein and Monk, 2017; Heany et al., 2018; Kraaijenvanger et al., 2020). Notably, negative findings also exist in the literature (e.g. Peters et al., 2019). A plausible explanation for our negative finding is that all patients, except one, in this study were treated with antidepressant drugs and antidepressant medication is known to dampen the activity of the amygdala in response to socio-affective stimuli (Sheline et al., 2001; Fu et al., 2004). Moreover, in our study, noises that can cause false activations in the amygdala region were rigorously filtered out, and F-test was applied when comparing study groups.

4.3. Correlation of clinical data with the BOLD response

In MDD + CM patients, a higher number of episodes was associated with increased BOLD response in the dorsal medial PFC (dorsal ACC and posterior paracingulate gyrus) that is involved in evaluative mechanisms and reappraisal of emotional stimuli (Etkin et al., 2011). Thus, MDD patients with childhood maltreatment presented a greater activation in this brain region parallel with the increasing number of episodes, which can be interpreted as a reaction to the illness progression in the maltreated group, where significant dysfunctions in regions of reward system, mood regulatory, and mentalizing networks were found in our sample.

On the other hand, in the MDD (without maltreatment) group, later onset of the illness was associated with a higher positive BOLD response in posterior temporal areas: posterior part of the medial and superior temporal gyri (BA21/22) involving the posterior sulcus temporalis superior which plays a central role in the integration of the face network (Wang et al., 2016). Hence, later onset of the illness implicates a better integration of the face network only in MDD patients without trauma.

4.4. Limitations

Our results should be interpreted in the context of limitations. This was a cross-sectional study with a relatively low number of subjects. The main reason for that was that we aimed to create rather homogenous and matched clinical groups. Since psychiatric comorbidities are higher in depressed patients with childhood maltreatment, it was not possible to exclude all MDD + CM patients with comorbid disorders, but comorbidities with relevant brain functional changes in regions involving emotional regulation were consistently excluded. Moreover, there was no study group with healthy controls with moderate or severe childhood maltreatment. Control subjects were also meticulously screened for any clinical symptoms. During recruitment, we identified only 4 individuals with no psychopathology and having been exposed to at least moderate level of the childhood maltreatment. As we could not extend this group, these four individuals were not enrolled in the study.

We assessed childhood maltreatment retrospectively and it has been shown that the congruence between retrospective and prospective measures can be poor or modest (Reuben et al., 2016; Baldwin et al.,

2019). Prospective, long-term studies, involving a larger number of individuals may yield different results. Furthermore, we did not assess the timing of adversity whereas, most likely the age at the time of abuse has significant importance.

Our main findings were the significant differences in negative BOLD responses, but the exact neurobiological mechanisms underlying negative BOLD responses are still uncertain. While earlier studies suggested that negative BOLD responses carry limited stimulus-specific information, a more recent study demonstrated that visual stimulation can evoke meaningful, stimulus-specific negative BOLD responses (Bressler et al., 2007).

Finally, the emotional face processing fMRI paradigms have been criticized for being unreliable as putative fMRI biomarkers (Nord et al., 2017). Patients with MDD were medicated with the most varied classes of antidepressants, sometimes combined with mood-stabilizing medications or augmented with atypical antipsychotics. Therefore, it was not possible to create homogenously medicated groups to control the effect of medication. Another problematic issue is whether one can unequivocally express his/her emotional state with facial movements, and how easily another person recognizes that.

4.5. Conclusions

MDD is a highly heterogeneous disorder and patients with a history of childhood trauma may either form a distinct subgroup within the illness (Heim et al., 2008), or there might be a dose-response relationship between cumulative childhood maltreatment and illness severity (Steine et al., 2017). In any case, the history of childhood maltreatment has significant implications for the clinical presentation (earlier onset, more severe MDD, more episodes, more suicidality, worse quality of life and functionality, and more psychiatric comorbidities), as well as for the treatment response (Medeiros et al., 2020; Negele et al., 2015; Nemeroff et al., 2003). Here, we found altered functioning of fronto-limbic reward and mood regulatory systems, as well as altered responses of mentalizing neural networks specifically in the MDD + CM subgroup. Our data support the concept that maladaptive processing of socio-emotional information might represent a pathway by which childhood trauma initiates a risk for psychopathology.

CRediT authorship contribution statement

Szilvia Anett Nagy: Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing - Original Draft. Zsófia Kürtös: Methodology, Investigation, Formal analysis, Visualization. Nándor Németh: Conceptualization, Methodology, Investigation, Formal analysis. Gábor Perlaki: Methodology, Writing - Review & Editing. Eszter Csernela: Investigation, Formal analysis. Flóra Elza Lakner: Investigation, Formal analysis. Tamás Dóczi: Supervision, Funding acquisition. Boldizsár Czéh: Conceptualization, Methodology, Resources, Writing - Original Draft, Writing - Review & Editing, Project administration, Funding acquisition, Supervision. Maria Simon: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Resources, Supervision.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

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