

Can psychopathy be prevented? Clinical, neuroimaging, and genetic data: an exploratory study

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ABSTRACT

The aim of the study was to explore the relationship among brain functional activations elicited by an emotional paradigm, clinical scores (PTSD, anxiety, and depression), psychopathic traits, and genetic characteristics (5-HTTLPR) in a group of severely maltreated children compared to a healthy control group before and after the implementation of a Trauma Focused-Cognitive Behavioral Therapy. The final sample consisted of an experimental group of 14 maltreated children (mean age = 8.77 years old, *S.D.* = 1.83) recruited from a non-governmental shelter in Mexico City for children who had experienced child abuse and a control group of 10 children from the general population (mean age = 9.57 years old, *S.D.* = 1.91). Both groups were matched according to age and gender and were assessed before and after the implementation of the aforementioned therapy by means of clinical scales and an emotional paradigm that elicited brain activations which were recorded through functional magnetic resonance imaging. Genotyping of the 5-HTTLPR polymorphism was made at first assessment. A region of interest analysis showed amygdala hyperactivation during exposure to fear and anger stimuli in the maltreated children before treatment. Following therapy, a decrease in brain activity as well as a decrease in clinical symptoms were also observed. 5-HTTLPR polymorphism did not show any effect on the severity of clinical symptoms in maltreated children. Trauma-Focused Behavioral Therapy may help reorganize the brain's processing of emotional stimuli. These observations reveal the importance of an early intervention when the mechanisms of neuroplasticity may be still recruited.

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Psychopathy is a developmental disorder characterized by callousness, a diminished capacity for remorse, impulsivity, and poor behavioral control (Decety et al., 2009; Frick, 1995; Hare et al., 1991). The emotional dysfunction component involves: reduced remorse and guilt, lack of empathy, and reduced attachment to significant others. The antisocial behavior component involves a predisposition toward antisocial behavior from an early age. It has been pointed out that traits which underpin psychopathy can be compartmentalized into roughly three categories including interpersonal traits (i.e., Grandiose-Manipulative), affective traits (i.e., Callous-Unemotional) and behavioral traits (i.e., Impulsive-Irresponsible) (Ribeiro da Silva et al., 2020).

Efforts to identify childhood precursors of psychopathy have revealed that callous-unemotional traits (CU) (i.e., low empathy/guilt, uncaring attitudes) are features that characterize individuals with a particularly severe, stable, and aggressive pattern of antisocial behavior (Viding & Kimonis, 2018). As a result of these studies, there have been several attempts to define if the developmental precursors of psychopathy aim to a better understanding of the causes of this disorder, as well as for improving designed interventions that could be implemented in the early stages of a child's development when the traits of psychopathy are presumably still malleable (Frick et al., 2016). Particularly, the development of CU traits that has been linked to both genetic and environmental risk factors; among the environmental adversities related to psychopathic traits are child maltreatment, harsh parental discipline, negative parental emotions, disorganized parent-child attachment, and disrupted family functioning (De Brito et al., 2021).

Furthermore, twin and adoption studies show evidence of genetic risk factors in psychopathic personality traits, particularly CU, suggesting that 50–80% of the individual differences are explained by genetic factors (Moore et al., 2019). There is also evidence of a shared genetic risk between a broader antisocial phenotype and CU traits. It has been suggested that risk factors which are considered to be environmental may be the result of the individual genetic vulnerability within biological families that may develop psychopathic behavior (De Brito et al., 2021; Viding et al., 2009).

Serotonergic neural projections in the hypothalamus, amygdala, and orbitofrontal cortex have been related to aggressive behavior suggesting that serotonin innervation is a neurotransmitter system worth analyzing in psychopathic traits (De Brito et al., 2021; Tielbeek et al., 2016). One of the most studied candidate genes in this system is the functional polymorphism of the promoter region of the serotonin transporter gene SLC6A4, namely the serotonin-transporter-linked promoter region 5-HTTLPR. This region is characterized by an insertion/deletion of a 20–23 base pair imperfect repeat sequence defining a short (S) and a large (L) allele related to the gain-of-function of the serotonin transporter promoter genotypes linked to obsessive-compulsive disorder (Hu et al., 2006).

From a genetic and neurobiological/hormonal standpoint, it was proposed that abusive experiences could induce a cascade of stress-mediated effects on hormones and neurotransmitters, which could then affect the development of vulnerable brain regions (Teicher et al., 2016). Early childhood is defined as the period of remarkable growth and brain development from birth to eight years old and maltreatment during this time could cause the inhibition of neurogenesis, an accelerated loss of neurons, delays in the myelination process, and alterations of the natural process of neuronal pruning (De Bellis, 2005; Mesa Gresa & Moya Albiol, 2011). It would appear that early adversity may increase the risk of altered brain maturation through an excessive release of glucocorticoids in different brain areas, as well as the risk of epigenetic

modifications that alter critical developmental processes (Lupien et al., 2009; Pechtel et al., 2014), including the exposure-sensitive periods of the amygdala, the hippocampus, the visual cortex, the prefrontal cortex (PFC) regions, and the inferior longitudinal fasciculus. These observations suggest that key circuit elements have relatively brief and unique periods of maximal susceptibility to maltreatment (Teicher et al., 2016).

Effective intervention programs for children who have been abused are one of the most important concerns when treating and reducing symptomatology, along with reducing emotional and cognitive impairments. To date, the most frequently used therapeutic approaches for children who are victims of abuse are psychoeducational, cognitive behavioral, psychodynamic, trauma centered, and play therapies (Hébert, 2020). The Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) which has now become the “gold standard” psychological treatment for pediatric PTSD is an evidence-based model of conjoint psychotherapy for children and parents/caregivers, for children and adolescents who are experiencing clinically significant emotional and behavioral difficulties related to traumatic life events. TF-CBT is a relatively brief (typically 12 to 20 sessions) component-based treatment model that incorporates interventions and techniques based on cognitive, behavioral, family therapy, and humanistic principles (Cohen & Mannarino, 1996). Up to date, numerous studies have documented the effectiveness of TF-CBT in helping children overcome these and other symptoms following trauma by helping them process their traumatic memories, overcome behavioral, and thinking problems, improve emotional regulation skills, and effectively develop interpersonal and coping skills (Cohen et al., 2011; Ready et al., 2015; Scheeringa et al., 2011; Smith et al., 2007).

Follow-up TF-CBT studies have shown a sustained benefit after 6 months, 1 year, and 2 years post-treatment (Cohen et al., 2006); however, TF-CBT neural foundations are insufficiently clear. Moreover, it is unknown if this type of treatment is effective for addressing distinct emotional deficiencies at the core of CU traits given their enduring nature and the developmental vulnerability of the brain during childhood.

Children and adolescents who were victims of maltreatment are more likely to develop PTSD, with 6% of maltreated children meeting criteria for PTSD (Kilpatrick et al., 2003). Models on the neurobiology and neurocircuitry of PTSD have been proposed to explain the substrate of symptomatology on emotional and cognitive difficulties (Admon et al., 2013; Akiki et al., 2017; Weems et al., 2018). Neurocircuitry models of PTSD (Admon et al., 2013) emphasize a hyperactivation of both the amygdala and the dorsal anterior cingulate cortex (ACC) as brain mediators of hypervigilance for threat and heightened anxiety, and a similarly hypoactive medial prefrontal cortex (mPFC) and hippocampus as brain mediators of deficits in emotion regulation and fear extinction.

Over the past three decades, extensive neuroimaging work has been devoted to the identification and characterization of functional and/or structural brain abnormalities in individuals with mental disorders, aiming to enhance the use of evidence-based practice in psychiatry (Insel et al., 2010). Research has focused on whether neurobiological changes which follow psychotherapy occur in regions that show significant pre-treatment neuro-functional alterations and whether these changes could be used as an objective index for monitoring the progress and outcome of psychotherapy (Thomaes et al., 2014).

The challenges that CU traits and psychopathy pose for intervention (Blair et al., 2014) and the enormous societal costs associated with antisocial behavior make it imperative to develop strategies for preventing the onset of CU traits in those at an increased risk.

The aim of this study was to explore the relationship among brain functional activation elicited by an emotional paradigm, and clinical (PTSD, anxiety, and depression), psychopathic traits, and genetic characteristics (5-HTTLPR) in a sample of a severe MC compared to non-trauma exposed HC before and after TF-CBT.

Materials and methods

Participants

Twenty-five children who suffered child abuse were initially recruited from a non-governmental shelter in Mexico City. Children were removed from their homes and placed at this shelter because one or both parents were undergoing judicial processes for various crimes, including child abuse. None of the children had ever received psychological therapy focused on trauma. After a thorough search for the most appropriate therapy, we concluded that the TF-CBT would serve these children best. This information was shared with the shelter administrative board. Once authorities and health professionals at the shelter were informed about the aim of the study, they agreed about the appropriateness of the intervention. A group of trained psychologists applied the TF-CBT as part of the research protocol. Only children who met the inclusion criteria participated. Parents or primary caregivers gave their informed written consent for their children to participate in the study.

The following flowchart specifies the number of participants enrolled in the study, reasons for dropout rates as well as the participants that completed the intervention and post-treatment assessment (Figure 1).

Ethical approval of the study was granted, and the research was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Trial registry www.clinicaltrials.gov; identifier NCT06028620.

Inclusion criteria

For the MC group, children whose ages were between 7 and 12 years old and who had a history of trauma or abuse, and high levels of PTSD (total score >11) and anxiety (total score >27) were included. Children were excluded from the study if they showed pervasive developmental delays or a history of psychotic symptoms or if substance abuse was documented in the institution files. Inclusion criteria for the HC group were ages between 7 and 12 years old, no history of trauma or abuse, and absence or low scores of PTSD (total score <10) and anxiety (total score <26) in the clinical assessment.

The final sample consisted of an experimental group of 14 MC which included 4 boys and 10 girls (mean age = 8.77 years old, *S.D.* = 1.83), who had experienced a positive history of different types of trauma, and a control group of 10 HC from the general population who were developing normally and were age-matched to the MC (4 boys and 6 girls) (mean age = 9.57 years old, *S.D.* = 1.91). The latter were recruited through an advertisement placed at the Faculty of Psychology, National Autonomous University of Mexico (UNAM) or by direct referral from parents of previous participants in other studies. All were residents of Mexico City. The study protocol was conducted with the approval of the UNAM Institutional Review Board.

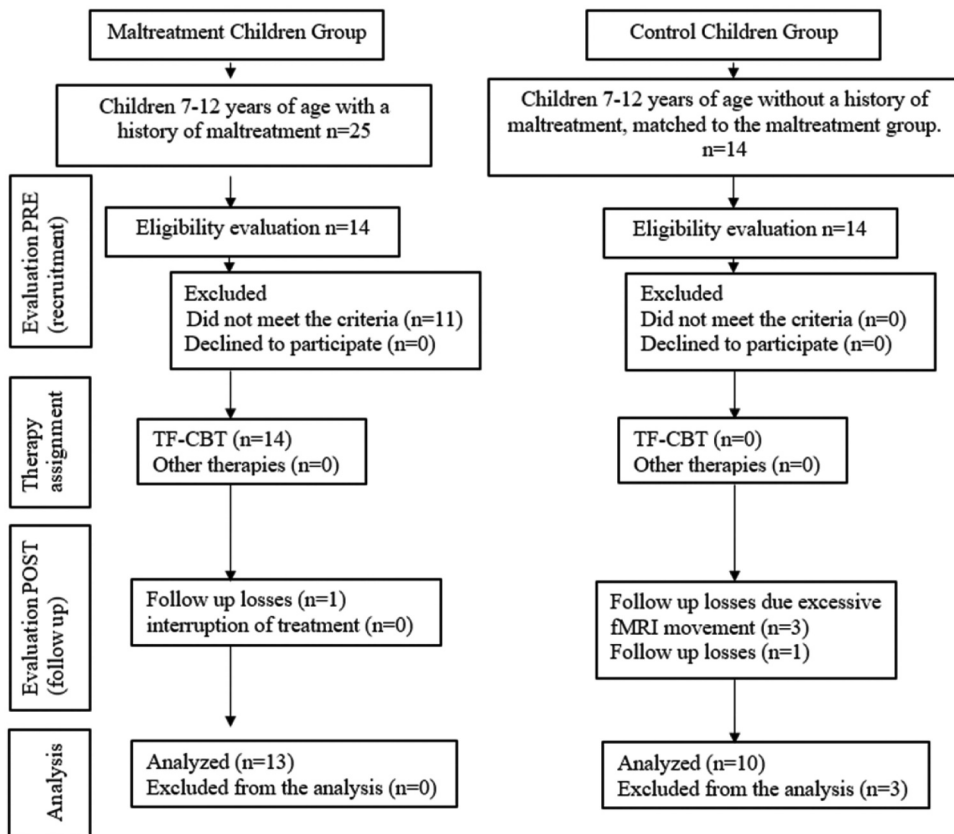


Figure 1. Flowchart of MC and HC enrolled in the study. Reasons for dropout rates as well as number of the participants (MC and HC) that completed the intervention and post-treatment assessment.

Intervention

Five psychologists were trained in TF-CBT according to an established protocol, which included completion of TF-CBT Web2.0 (accessible at <https://tfcbt2.musc.edu/>), an online resource for TF-CBT training. For this study, 12 to 16 60–90 min sessions were implemented once a week for 4 months. Of the total sample, 14 MC completed the TF-CBT modules and came in for their post-treatment assessment session. In addition, the 10 HC who, according to their parents, had not undergone any type of psychological intervention during those 4 months, and still met the inclusion criteria for the initial control group were selected and returned for their post-evaluation session. **Figure 2** describes the components of the TF-CBT protocol.

Type of data

The MC group was assessed before and after the implementation of TF-CBT, with a 6 months interval, using clinical scales, an emotion paradigm through functional magnetic resonance imaging (fMRI) and genetic data. The HC group was also assessed with the same indicators twice, respecting the 6 months interval.

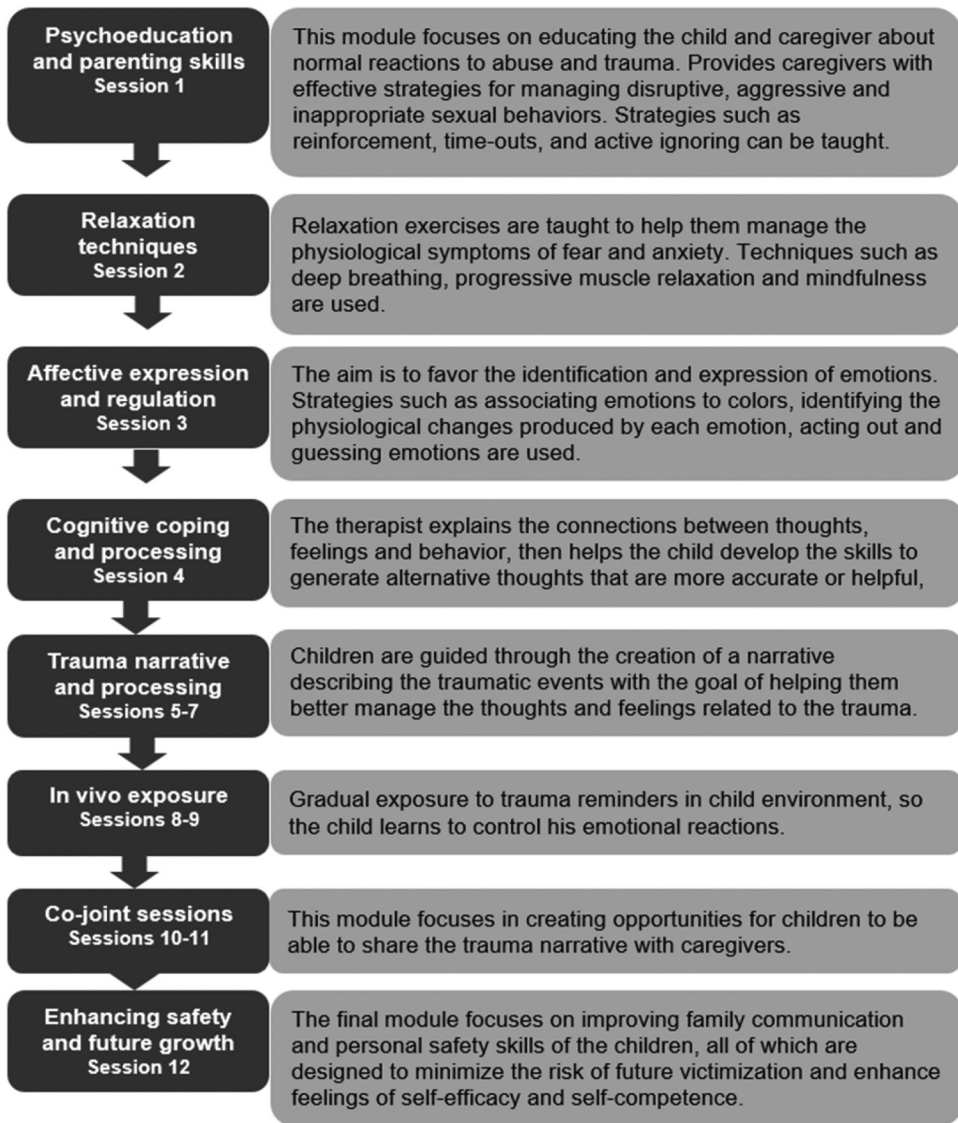


Figure 2. Components of the TF-CBT protocol. Adapted from Child Welfare Information Gateway (2012). Trauma-focused cognitive behavioral therapy for children affected by sexual abuse or trauma.

Clinical

A comprehensive clinical battery was used to assess all participants pre and post treatment, through the administration of the following assessment tools: The Child Depression Inventory (CDI) Spanish version (Del Barrio & Carrasco, 2004). The Spence Children's Anxiety Scale (SCAS) standardized on a sample of Mexican children by Hernández et al. (Hernández-Guzmán et al., 2010), the Child PTSD Symptom Scale (CPSS) Spanish version (Bustos et al., 2009), and the Inventory of Callous Unemotional Traits (ICU) Spanish version (López-Romero et al., 2015) including the total score and three subscales for callousness, uncaring, and unemotional (Frick, 2004).

Neuroimaging

Stimuli were presented with E-prime software (Psychology Software Tools, Inc. Pittsburgh, PA, USA) through a back-projection system. We developed an emotion observation task taken from the Amsterdam Facial Dynamic Facial Expression Set (AFDES), a standardized video set of emotion-dynamic facial expressions (Van der Schalk et al., 2011; Wingenbach et al., 2016). We selected video stimuli depicting expressions of three males and three females expressing anger, happiness, fear, and neutral emotions that quickly evolved into a full-blown emotional expression of high intensity, or remained still in the case of neutral stimuli. Our optimized set included four 18-sec video clips per emotion, two per gender. To verify that participants were paying attention to the task, we created three neutral catch trials with an additional visual distortion in the last face stimulus of the block that participants had to count and verbally report at the end of each session. Accordingly, our fMRI paradigm consisted of four blocks of facial expressions of each emotion that participants observed twice across two 8-minute-long experimental runs (r1, r2), for a total of 8 blocks per emotion observed in a pseudo randomized fashion. Each run included 19 blocks: 16 emotion stimuli blocks (4 per emotion) plus 3 catch trial blocks. Actors' presentation order was counterbalanced across blocks of different emotions. Blocks were jittered with a mean intertrial interval of 8 sec (ranging from 7–9 sec) and the total task duration was approximately 17 min.

Neuroimaging data acquisition. All images were acquired using the 3.0 Tesla Achieva MRI scanner (Philips Medical Systems) with an 8-channel head coil at the Centro Nacional de Investigación en Imagenología e Instrumentación Médica (CI3M) in Mexico City. The MRI protocol involved the acquisition of two runs of task-based fMRI to measure bold signal changes between task-stimulated states and control states as well as T1-3D anatomical images for both pre- and post-moments. For task-based fMRI functional images, volumes were acquired using an EPI sequence with the following parameters: TR/TE = 2000/27 ms; flip angle = 90°; FOV = 80 mm; matrix = 96 × 96; in plane resolution = 2.75 × 2.75 × 2.75 mm; number of volumes = 246; number of slices = 39; orientation = axial; order of acquisition = interleaved. Parameters for anatomical T1-3D were: TR/TE = 7.12/3.5 ms; flip angle = 8°; FOV = 240 mm; matrix = 240 × 240; in plane resolution = 1.04 × 1.04 × 1.1 mm.

Genetic data

We obtained a sample of buccal epithelial cells from MC and HC participants. The extraction of DNA was performed using the Gentra Puregene Buccal Cell Kit (QuiagenMR) according to the manufacturer's protocol.

Genotyping of the 5-HTTLPR polymorphism was performed using the primers and the conditions previously reported (Heils et al., 1996). PCR products were resolved on 1.5% high-melt agarose gels containing ethidium bromide and visualized under UV illumination.

Data analysis

Clinical data analysis

Statistical analysis was carried out using the Statistical Package for Social Science (SPSS 22.0 for Windows). A Mann-Whitney U test was used to compare the clinical measures between

maltreated and control groups on the pretest evaluation. To assess the differences between pre and post treatment on clinical measures, a Wilcoxon test was used and in order to identify clinical improvement, a reliable change index (RCI) was calculated for each clinical measure in MC group. This index determines whether the magnitude of change for a given participant is statistically reliable, thus reflecting that changes are not due to fluctuations of an imprecise measuring instrument. When the RCI is greater than 1.96, it is unlikely that the posttest score is not reflecting a real change (Jacobson & Truax, 1991).

Neuroimaging data analysis

In order to assess the impact of changes in clinical measures and also changes in neuroimaging activations, score differences (DIF) were obtained by subtracting pre-scores from post-scores. We also studied neurobiological treatment effects and correlations between clinical improvement and changes in regional blood oxygenation level-dependent (BOLD) responses during the emotional processing task; $p < .05$ was considered statistically significant.

Functional data were analyzed using the pipeline suggested in SPM12 and related toolboxes (Wellcome Department of Imaging Neuroscience <http://www.fil.ion.ucl.ac.uk/spm>). The first five volumes of each run were discarded to allow for T1 equilibration effects. Outlier functional scans and slices were repaired with the Artifact Repair Toolbox (Gabrieli Cognitive Neuroscience Lab; <http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm>), after which the images were slice-time corrected, taking the middle slice as reference, and then realigned to the first image in the session. The anatomical T1 was co-registered (Collignon et al., 1995) with the mean image calculated from slice-timed and realigned functional scans. Each participant's T1 scan was normalized to the MNI-space. A mass univariate general linear model (GLM) was applied, using each stimulus type regressor obtained by convolving the canonical hemodynamic response function (provided by SPM12) with delta functions at stimulus onsets, and also including the six motion-correction parameters as covariates. After preprocessing, a first-level analysis was performed on each subject with the GLM. A t-statistic was obtained at each voxel for each of the emotional face conditions (anger, fear, happiness, and neutral).

Regions of interest analysis. For the regions of interest (ROIs) analysis, we used Neurosynth, a platform for large-scale automated synthesis of fMRI data, to identify voxels within the brain that have been previously associated with emotion (Yarkoni et al., 2011).

To define ROIs, we queried the NeuroSynth database (neurosynth.org) for regions responding to emotional faces. The term “emotional faces” was used for generating a map in Neurosynth, outwardly revealing brain regions from the neuroimaging literature that show a significant meta-analytic association with this term. This search evinced 11 ROIs which were named according to their anatomical location in the Automated Anatomical Labeling (AAL) atlas of the human brain: left amygdala, right amygdala, left insula, right insula, left fusiform face area (FFA), right FFA, left frontal inferior pars triangularis, right frontal inferior pars triangularis, left frontal superior medial area, left putamen, and right frontal inferior operculum. Functional measures were extracted from these ROIs by averaging the values of each contrast (anger, fear, happiness, and neutral) across the voxels in each ROI. This procedure was applied to each subject's fMRI data obtained pre- and post-therapy. For

each emotional face condition, comparisons among groups (MC vs. HC) and time (pre- and post-therapy) were tested by analysis of variance (ANOVA).

In order to assess the impact of changes in clinical scales with changes in neuroimaging data, score differences (DIF) were obtained by subtracting pre-scores from post-scores. A Spearman's correlation was used to measure the strength and direction of the monotonic relationship between them ($p < .05$).

Genetic data analysis

Hardy-Weinberg equilibrium was tested with the HWE software. Genotype and allele frequencies of both MC and HC were analyzed with χ^2 test using the Epidat Version 3.1 software. ANOVA and t-Student analysis were performed with the SPSS software v.20.0 (SPSS software, IBM, New York, NY, USA).

Results

Baseline differences between groups and types of abuse

Before entering the shelter, our sample of MC had experienced severe abuse since early childhood (mean 4 years of age) and had lived in a violent and poor environment that was so bad that in 80% of the cases parents had been sent to prison for committing childhood abuse among other crimes.

MC group reported different types of abuse, including neglect (100%), physical (57.1%), emotional (42.8%), and sexual abuse (35.7%). Note that the sum of the percentages of the types of abuse exceeds 100% because a significant proportion of participants (57.1%) had experienced multiple types of trauma. The characteristics of the sample are presented in [Table 1](#).

Pre- and post-treatment clinical tests

Clinical inventories

As reported in [Table 2](#), MC group obtained higher significant scores than HC group for all clinical measures. The MC group was characterized by high levels of anxiety, depression, and PTSD, symptoms which have been reported in other studies. Likewise, CU traits were also higher for this group in comparison to the HC group.

To explore the evolution of the MC group following treatment, differences between pre-treatment and post-treatment scores were compared using a Wilcoxon test. Results revealed significant differences in the MC group clinical characteristics, such as reduction of PTSD symptoms, depression, total CU scores, and uncaring and unemotional traits ([Table 3](#)). No significant differences in anxiety and callous trait scores were found. In addition, we calculated a RCI to identify which participants showed a significant clinical change. RCI greater than 1.96 was considered as significant. In the MC group 50% of the participants improved on the Anxiety Scale, 64% improved on PTSD scale, 71% on the CU total score, and 64% and 71% improved on Uncaring and on Unemotional subscales of CU, respectively. Negative RCI reflect clinical traits that diminished after treatment ([Table 4](#)).

Table 1. Baseline differences between groups.

Participant Characteristics		
	HC N = 10	MC N = 14
Sex (M/F)	4/6	4/10
Age (years) Mean (s.d.)	9.3 (1.9)	8.7 (1.8)
<i>Type of trauma (Percentage)</i>		
Sexual abuse	-	36
Physical abuse	-	57
Neglect	-	100
Emotional abuse	-	42
<i>Identity of the perpetrator</i>		
Immediate family	-	50
Extended family	-	28.5
Known perpetrator	-	42.85
Stranger	-	0
<i>Duration of the abuse</i>		
Few episodes		
Emotional abuse	-	78
Physical abuse	-	42
Chronic		
Neglect	-	100
Physical abuse	-	6.25

Types of abuse, in the MC group, the sum of the percentages of the types of abuse exceeds 100%, because 57.1% of the participants had experienced multiple types of trauma.

Table 2. Pre-treatment clinical characteristics of maltreated vs healthy control group.

Variable	Maltreated group		Healthy control group		z	p
	Mdn	Range	Mdn	Range		
Anxiety	42.5	17.29	18	5.80	-3.927	.001**
Depression	15	16.82	8.5	6.45	-3.563	.001**
PTSD	23	17.50	4	5.50	-4.106	.001**
CU	45	17.50	9	5.50	-4.101	.001**
Uncaring	18	17.46	4	5.55	-4.086	.001**
Callous	18	17.39	1.5	5.65	-4.021	.001**
Unemotional	15	16.89	3.5	6.35	-3.621	.001**

Mdn: median; PTSD: Post-Traumatic stress disorder; CU: Callous-Unemotional Traits.

Table 3. Pre and post treatment clinical characteristics of the MC group.

Variable	Pre-treatment		Post-treatment		z	p
	Mdn	Range	Mdn	Range		
Anxiety	42.5	17.29	30.5	73	-1.320	.187
Depression	15	16.82	12	17	-2.437	.015**
PTSD	23	17.50	13.5	26	-2.665	.008**
CU	45	17.50	32.5	50	-2.926	.003**
Uncaring	18	17.46	15	19	-2.949	.003**
Callous	18	17.39	9.5	23	-0.946	.344
Unemotional	15	16.89	11.5	13	-2.946	.003**

Mdn: median; PTSD: Post-Traumatic stress disorder; CU: Callous-Unemotional Traits.

Table 4. Reliable change index in clinical scales for MC group.

Subject	Anxiety	Depression	PTSD	CU	Uncaring	Callous	Unemotional
1	-2.73*	-2.46*	-3.93*	-3.15*	0.00	-1.03	-5.74*
2	3.07	-0.82	0.91	-1.75	-3.16*	1.03	-3.28*
3	-1.37	0.00	-3.93*	-4.20*	-5.26*	-1.54	-3.28*
4	-3.07*	-8.61*	-6.04*	-5.59*	-5.26*	-6.15*	0.82
5	-3.58*	-2.05*	-5.14*	-8.74*	-9.47*	-4.10*	-6.56*
6	-3.41*	-4.51*	-5.74*	-4.20*	-4.21*	1.03	-8.20*
7	1.19	-1.64	-2.11*	-3.15*	-1.05	-2.56*	-2.46*
8	4.44	1.23	-3.93*	-1.75	-3.16*	2.05	-4.92*
9	-0.17	-4.92	-3.93*	-3.85*	-3.16*	-1.54	-4.10*
10	-3.41*	0.00	-0.60	1.75	0.00	2.56	0.00
11	-0.17	-1.23	-3.02*	-4.20*	-4.21*	-2.56*	-2.46*
12	-2.90*	-2.05*	-1.81	-2.80*	-4.21*	-2.05*	0.00
13	-2.73*	1.23	0.00	-0.35	0.00	2.05	-4.10*
14	1.54	-0.82	3.02	0.70	-1.05	2.05	-0.82
<i>Improvement</i>							
Frequency	7	6	9	10	9	4	10
Percentage	50	42	64	71	64	28	71

*>1.96. A Negative index reflects improvement. PTSD: Post-Traumatic stress disorder; CU: Callous-Unemotional Traits.

Neuroimaging

Brain activity differences between maltreated and healthy control groups

The ROI analysis of hemodynamic response between MC and HC groups was measured from the group and emotion by ROI interaction (Figure 3). These values were included in the ANOVA test (for group, emotion, and ROI as factors).

Simple main effects analysis showed that groups have a statistically significant effect ($F(1, 30) = 4.46, p = .043$). For the interaction between groups, emotion and ROI were

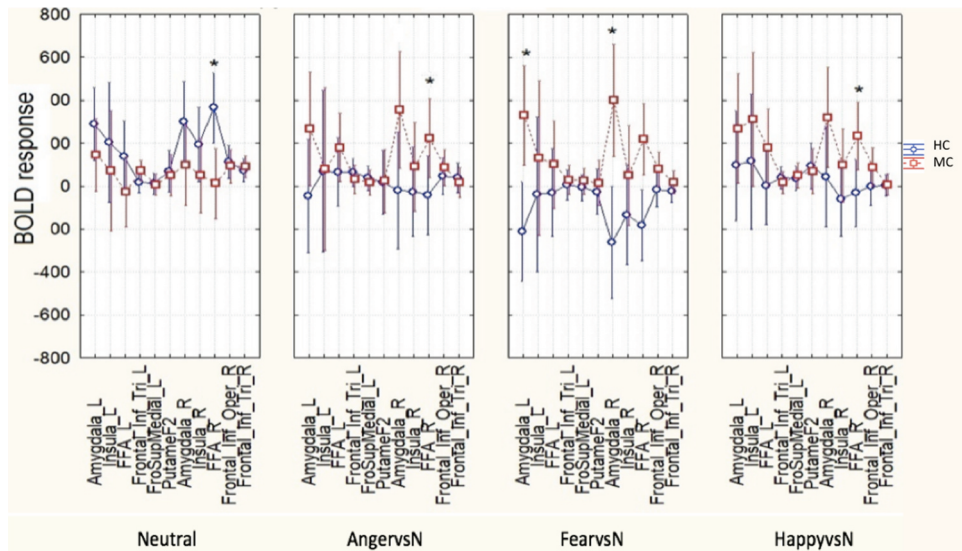


Figure 3. Functional ROIs from Neurosynth (emotional faces) before therapy. Activation in the following regions bilateral amygdala, insula, FFA, frontal inferior operculum (FIO), and frontal inferior pars triangularis (FIT) and putamen is shown for processing neutral, anger, fear, and happiness emotions.

significant ($F(30, 900) = 1.96, p = .001$) (H-F correction: $\epsilon = 0.23$, adjusted $p = .17$). Planned comparisons showed that differences between MC and HC pre-therapy were significant for the right Fusiform Area (FFA) ($F(1, 30) = 8.77, p = .005$) for the neutral expression and the anger emotions ($F(1, 30) = 4.45, p = .043$) as well as for the happiness emotion ($F(1, 30) = 4.38, p = .044$), and for the left amygdala ($F(1, 30) = 9.074, p = .005$) and right amygdala ($F(1, 30) = 10.97, p = .002$) for the fear emotion.

A more detailed analysis of changes in ROIs activations associated with TF-CBT was performed for pre- and post-therapy measurements in ROIs obtained from the time group by emotion interaction (Figure 4). These values were included in the ANOVA test with group, time, ROI, and emotion as factors.

Simple main effects analysis showed that ROI had a statistically significant effect ($F(10, 210) = 12.046, p < .001$) (H-F correction: $\epsilon = 0.34$, adjusted $p = .0015$). The interaction between ROI and emotion was significant ($F(30, 630) = 1.517, p = .039$).

Comparisons for each ROI showed significant interactions for the time (1-1) group (1-1) only for fear emotion (Figure 5) in the left amygdala ($F(1, 21) = 7.68, p = .011$), the left FFA ($F(1, 21) = 5.72, p = .026$), and the right FFA ($F(1, 21) = 8.62, p = .007$), the right FIO ($F(1, 21) = 4.83, p = .039$) (H-F correction: $\epsilon = 0.34$, adjusted $p = .026$) and the right FIT ($F(1, 21) = 9.29, p = .006$).

We conducted an additional analysis to further investigate the specificity of the relationship between the signal change and symptoms reduction of PTSD, ICU, depression, and anxiety associated with treatment. There was a significant positive correlation between symptoms decline and reduction in brain activity (post-pre) in the left amygdala ($p < .016$), right FIO ($p < .038$), right FIT ($p < .013$) for ICU (uncaring); and the putamen ($p < .013$), left frontal superior medial area (FSMA) ($p < .001$), right FIT ($p < .05$), and right amygdala ($p < .24$) for anxiety.

Genetic analysis

Genetic analysis of 5-HTTLPR polymorphism in the MC group showed a frequency of SS, SL, and LL alleles of 0.25, 0.25, and 0.50, respectively; and in the HC group a genotype frequency of 0.10, 0.45, and 0.45, respectively. Therefore, we did not find any statistical difference between MC and HC ($\chi^2 = 1.88, p = .39$).

We analyzed the effect of S allele carriers of the 5-HTTLPR polymorphism on the clinical scores of anxiety, depression, PTSD, and ICU traits between mean pre and post treatment measurements. In the MC, the S allele carriers (SS+SL) showed a decrease in total ICU scores after therapy treatment ($t = 4.5, p = 0.006$) (Figure 3). However, there were no statistical differences for anxiety ($t = 0.96, p = 0.38$), depression ($t = 1.61, p = 0.166$), and PTSD ($t = 2.11, p = .089$) symptoms between pre and post treatment scores. Also, analysis of the L allele carriers in the MC (SL+LL) showed statistical differences for total ICU scores after treatment ($t = 0.87, df = 7, p = .035$) and PTSD scores ($t = -0.18, df = 7, p = .023$), suggesting that the decrease in the clinical characteristics is related to treatment.

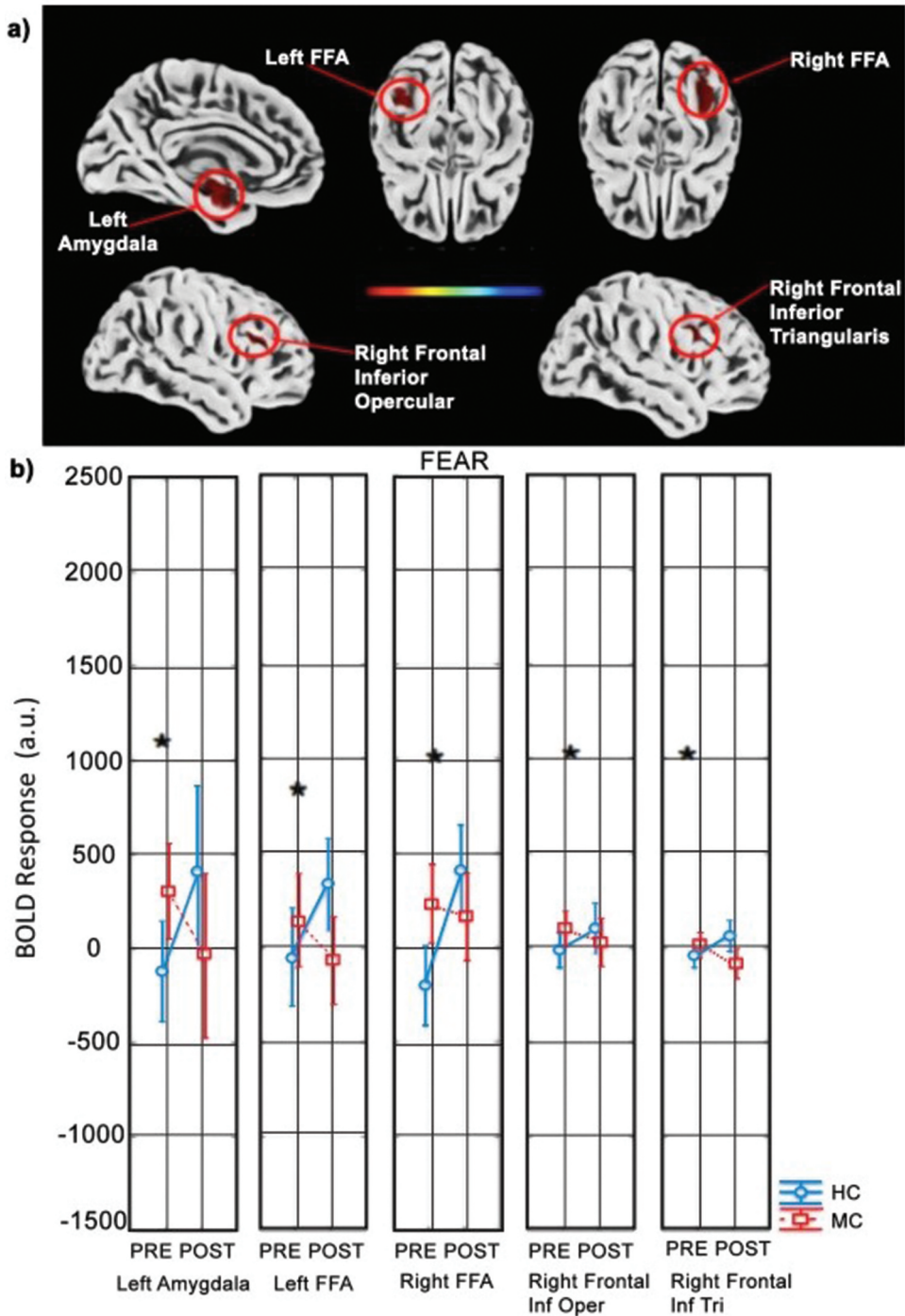


Figure 4. Activation in left amygdala, bilateral FFA, right FIO, and right FIT in fear emotions processing before and after therapy. (a) Graphical depiction of significant ROIs activations showing differences after the TF-CBT. (b) Significant differences before and after therapy on activation by processing fear.

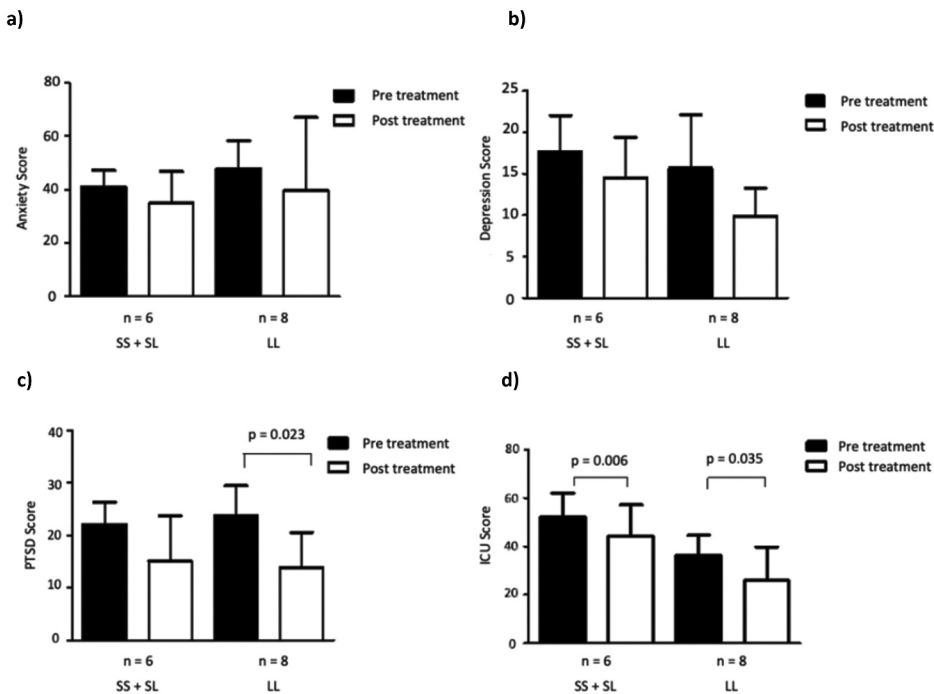


Figure 5. Pre and post treatment analysis of the effect of the S and L 5-HTTLPR variants on clinical characteristics of allele carriers. Means and SD in S and L allele carriers for: (a) anxiety scores; (b) depression scores; (c) PTSD scores; and (d) total ICU scores.

Discussion

The aim of the study was to explore the relationship among brain functional activation elicited by an emotional paradigm, and clinical scores (PTSD, anxiety, and depression), psychopathic traits, and genetic characteristics (5-HTTLPR) in a group of severe MC compared to HC group before and after TF-CBT. Following a discussion of clinical, neuroimaging, and genetic data is presented as well as the correlations among the different data.

Clinical data

After therapy, there was a clinical decrease on ICU scores as well as PTSD and depression symptoms. Although the scores of the MC group are not equal to the scores of the HC group, it is a positive outcome for the individuals, considering the multiple types of abuse they have endured as well as their exposure time, factors that have been shown to aggravate the consequences of maltreatment (Patriat et al., 2016; Weems et al., 2018).

The RCI analysis identified which participants showed significant clinical changes. In the MC group, 50% of the participants improved on the Anxiety Scale, 64% improved on the PTSD scale, 71% on the CU total score and 64% and 71% improved on Uncaring and Unemotional subscales of CU respectively.

Our results are in line with previous studies showing that TF-CBT is effective in treating and reducing symptoms related to childhood maltreatment (Deblinger et al., 2011).

Neuroimaging data

Pre-treatment differences between MC and HC groups were significant in several areas that are crucial for interacting appropriately in social situations, including the right fusiform area while processing neutral, anger, and happiness emotions, and the left amygdala for handling fear emotions. After therapy, the MC group showed significant changes in the activation of the left amygdala, bilateral fusiform area, right frontal inferior operculum, and the right frontal inferior pars triangularis during the processing of fear, but exhibited no differences when compared to the HC group. These results suggest that TF-CBT normalized altered brain structures in MC.

Abnormal neural responses to other emotions, particularly cues to threat and distress, have been implicated in the development of chronic violence. According to Blair (2008), emotional facial recognition is a pre-requisite for the development of the affective components in the empathy construct. Decety (2015) pointed out that individuals with psychopathy fail to recognize the codes that would help them inhibit their aggressive behavior by activating the neural circuits involved in the process that activates automatic versus goals directed attention. It was also postulated that these significant deficits for emotional facial recognition are the result of a dysfunction of the amygdala (Blair et al., 2004). In sum, this prevents individuals with psychopathy from obtaining associative knowledge in the process of conditioning stimuli, such as fear and sadness, thus resulting in empathic impairments and inappropriate social behaviors toward others.

Genetic data

Genetic analysis of 5-HTTLPR polymorphism in the MC and HC groups did not show any statistically significant differences between them.

Correlations between the different types of data

Our findings showed significant positive correlations between symptoms decline in psychopathic traits, depression, and PTSD and a reduction in brain activity (post-pre) in the left amygdala, right frontal inferior operculum, right frontal inferior pars triangularis with uncaring, and in the putamen, left frontal superior medial area, right frontal inferior pars triangularis, and right amygdala with anxiety.

These results are consistent with the hypothesis that an improvement in clinical symptoms can lead to an improvement in self-regulation involving common brain functions and networks. More specifically, a change may occur after TF-CBT when recalling the traumatic event as MC worked on narrating their traumatic experience as required by the TF-CBT. Through work on modifying their thoughts and developing coping strategies in MC, the function of the limbic and the hippocampal structures may be modified, thus making down regulation more efficient by improving communication

between the brain networks. Consequently, the approach of the TF-CBT confronts the clinical and the neurobiological changes present in the maltreated population, which could explain the changes observed in the ROIs and in networks as it is usually mentioned in the literature (Akiki et al., 2017; Weems et al., 2018). Furthermore, specialized research has shown that there is a neurofunctional alteration in MC group with PTSD and low emotional regulation that involves regions and networks such as the limbic system, the hippocampus, and the prefrontal cortex which in addition to being the substrate for clinical symptoms are also part of the network implicated in cognitive functions such as executive functions, declarative memory, emotion recognition, etc. (Bustos et al., 2009). A better understanding of the impact of psychotherapy on brain function will eventually result in the development of an effective rehabilitation protocol (Admon et al., 2013; Akiki et al., 2017; Weems et al., 2018).

It has been pointed out that stability estimates and the analysis of developmental trajectories indicate that CU traits in youth are variable, not constant (Viding & Kimonis, 2018). Critical factors are parental attachment and involvement. In our sample, the children were living in a shelter and assisted by trained caregivers while receiving the TF-CBT intervention. The behavioral phenomena targeted in TF-CBT (e.g., heightened anxiety, affect dysregulation, deficits in cognitive coping skills) closely resemble the functional attributes of the PTSD neurocircuitry. Given the overlap between the behavioral targets of TF-CBT and the neuroanatomy of PTSD one could expect that a clinical response to TF-CBT would be related to pre-treatment variability within this neurocircuitry.

Regarding the effects of therapy and the correlations between clinical improvements and changes in the regional blood oxygenation level-dependent (BOLD) signal during the emotional processing paradigm, we found a significant positive correlation between ICU and anxiety symptoms decline and larger decreases in brain responses in several regions, including the bilateral amygdala, the right frontal inferior operculum, the right frontal inferior pars triangularis, the left frontal superior medial area, and the putamen. After the TF-CBT intervention, a decreased activity may be interpreted as “normalized” activity, indicating more cognitive control over clinical symptoms.

The genetic analyses revealed that a decrease in the scores for the clinical characteristics that only showed statistical significance for the total ICU and PTSD scores in the S and L allele carriers, suggesting that the 5-HTTLPR polymorphism may not influence the severity of clinical symptoms in subjects exposed to maltreatment. However, our study should be extended to a larger sample size to understand the role of the SLC6A4 gene in the development of psychopathologic traits in children living in adverse environments.

Limitations

The present study has several limitations. First, we evaluated a relatively small sample with severe maltreatment due to the difficulties associated with recruiting very young children, in fact, when reviewing the literature, we mainly found samples of adolescents and adult subjects.

Second, the sample was heterogeneous since children endured various types of maltreatment concurrently; therefore, we cannot discuss the effect of a specific type of abuse, future research should address this issue. Also, all MC in our sample showed PTSD

symptoms, therefore our study did not provide information on the effect of maltreatment without the presence of post-traumatic stress.

Finally, another factor to consider is that the HC group was not subjected to any therapy, which prevents controlling for other nonspecific treatment-related factors that could have potential effects on brain functional activations. Also, we were not able to recruit a MC control sample with children from the shelter that did not receive therapy (waiting list group), this is an important limitation. However, the MC sample was removed from their homes and placed at this shelter because one or both parents were undergoing judicial processes for various crimes, including child abuse. All of them had a minimum of 4 years living in the shelter and none of the children had ever received any psychological therapy focused on trauma. The only change that occurred in that period of time was the TF-CBT intervention. Although many MC participants showed an improvement in most clinical scales, they did not reach the scores obtained by the HC participants. The treatment had an impact on their psychological characteristics; however, these individuals need further psychological care in order to get a better functional adjustment. Although CU traits are being vastly studied as “precursors of psychopathy,” several research studies have also pointed out that psychopathic traits tend to be associated as reviewed by Ribeiro da Silva et al. (2020). These traits can be compartmentalized into roughly three categories including interpersonal traits, affective traits, and behavioral traits. Further studies should include these psychopathic traits.

All these methodological aspects should be taken into account in future studies. Additionally, long-term follow-up scans will be necessary in the future to determine if changes in fMRI measurements persist over time.

Future research

With the purpose of extending the knowledge of this study, we suggest that in the future this research should be replicated with a larger sample and at the same time behavioral problems should also be evaluated.

In conclusion, our results suggest that the effect of maltreatment in very young children could be reversed by therapeutic interventions. The differences between MC and HC before therapy were significant in several areas that are crucial for interacting appropriately in social situations. In particular, after therapy, the MC group showed significant neural changes to fear-presenting stimuli. Our research certainly adds to the growing body of knowledge on the neurobiological impacts of child maltreatment and offers hope for the potential reversibility of these effects through therapeutic interventions.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval and consent to participate

A signed informed consent form was obtained from all parents, and Ethical approval of the study was granted by the UNAM Institutional Review Board, and the research was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was registered as a clinical trial at www.clinicaltrials.gov with identifier NCT06028620.

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