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ORIGINAL PAPER

Increased recruitment of cognitive control in the presence of traumatic stimuli in complex PTSD

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Abstract A neurocircuitry model of post-traumatic stress disorder (PTSD) suggests increased amygdala responses to emotional stimuli, coupled with hypoactivation of prefrontal regions associated with cognitive control. However, results are heterogenous across different subsamples of PTSD as well as different paradigms. We investigated cognitive control in a classic and emotional Stroop task in 28 female patients with complex PTSD (cPTSD), 28 female trauma-exposed healthy controls (TCs) and 28 female non-trauma-exposed healthy controls (HCs) using functional neuroimaging. Afterwards, we assessed memory function in a spontaneous free recall and recognition task. Patients with cPTSD displayed significantly greater Stroop interference with trauma-related words (as reflected in slower reaction times and increased errors) compared to the other conditions and compared to the TC and HC groups. Moreover, patients with cPTSD showed increased activation in the context of trauma-related words in brain regions associated with cognitive control (dlPFC, vmPFC, dACC) compared to both control groups, and a trend for increased activation in the insula compared to the HC group. Increased recruitment of regions contributing to cognitive control in patients with cPTSD, together with a lack of amygdala response may point to efforts to compensate for emotional distraction caused by the trauma-related words.

Keywords Complex post-traumatic stress disorder · Child abuse · fMRI · Stroop task · Cognitive control

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Introduction

The cross-national lifetime prevalence of post-traumatic stress disorder (PTSD) is estimated to be about 3.9% [1]. However, far more individuals experience a traumatic event in their lifetimes [1]. Those who develop PTSD in the aftermath of childhood interpersonal violence not only show the hallmark symptoms of PTSD such as intrusions, avoidance, numbing and hyperarousal, but usually also a range of further symptoms which include interpersonal problems, dissociative features and severe problems in emotion regulation [2]. This syndrome has been described as complex PTSD (cPTSD) [3] or as 'PTSD with associated features' [4]. PTSD represents an important mental disorder per se and also a frequent co-morbid disorder in a variety of clinical groups [5, 6]. It has been suggested that one factor leading to the maintenance and exacerbation of PTSD symptoms (e.g., hypervigilance, intrusive thoughts and flashbacks) may be the increased attention to threatening stimuli [7, 8]. Likewise, impaired response inhibition of threat stimuli might reflect impaired cognitive control (i.e., inhibition of distracting stimuli). Widely used methods to study cognitive control are the classic Stroop task [CST; 9] and the emotional Stroop task [EST; 10]. The subject has to name the colour of a word as quickly as possible, ignoring the semantic content of the words. Usually, reaction times are increased for incongruent words (e.g., 'blue' written in red) and emotionally charged words (e.g., 'attack'), especially when emotional words are related to the patient's psychopathology.

Several hypotheses have been developed for the classic and emotional Stroop effect. While the CST examines the general interference between conflicting processes (the tendency to say the name rather than the colour), the EST assesses an attentional bias (increased selective attention) of the processing of individual-relevant information or an inability to inhibit individual-relevant information [11]. Studies have repeatedly found that patients with PTSD exhibit impaired performance in both the CST [12] and EST compared to trauma-exposed healthy controls [TCs; 13, 14] and non-trauma-exposed healthy controls [HCs; 15, 16]. These results suggest generally impaired inhibitory functions as well as an attentional bias to negative-valenced and especially trauma-related words compared to neutral words in patients with PTSD. However, others did not find impairments compared to TC [17] and HC groups [18]. Related to the assumption of increased attention to threatening stimuli in patients with PTSD, multiple studies examined memory processes. Evidence was found for a memory advantage in PTSD vs controls for negative threat information [19] as well as an attentional bias for trauma-related material [14]. Others did not find any differences in memory functions between patients with PTSD and controls [e.g., 20]. A variety of functional neuroimaging studies (fMRI) using Stroop-type paradigms have been used to examine brain correlates of cognitive control in PTSD (e.g., accidents or combat) and have shown increased amygdala responses to emotional words [e.g., 21] and disrupted recruitment of prefrontal regions associated with cognitive control, especially in the presence of emotional distracters [22, 23]. These results led to the formulation of a neurocircuitry model of PTSD [for review see: 24]. This model suggests hypoactivation of prefrontal regions associated with cognitive control {dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex [vmPFC, including rostral anterior cingulate cortex (rACC)]} which results in an inability to regulate affective areas (amygdala), leading to exaggerated fear response [e.g., 25, 26]. Although this model did not originally include the dorsal ACC (dACC) and the insula, emerging evidence suggests that these regions may be hyperresponsive in PTSD and may also play an important role in this disorder [27–29]. However, only two studies have investigated Stroop-tasks in childhood abuse-related patients with PTSD [15, 30], reporting conflicting findings. In the EST, Bremner and colleagues [30] observed increased dACC activation with decreased rACC and posterior insula activation in patients with PTSD compared to the TC group. Thomaes et al. [15], who used a hybrid version of the CST and EST in cPTSD patients, found no significant group differences between patients with cPTSD and the HC group in the EST. In the CST, patients showed a trend for increased left anterior insula and dACC activation compared with the HC group [15]. It is possible that differences in comparison groups (TC vs HC) account for these divergent findings. One limitation of the previous fMRI studies is the absence of both matched HC and TC groups. The inclusion of both control groups provides us with the opportunity to explore whether neural abnormalities are associated with PTSD symptoms or result from the experience of the trauma alone.

Based on previous findings, the present study was designed to examine differences in brain activity in patients with childhood-abuse-related cPTSD, TC and HC groups using a hybrid version of the CST and EST (CEST) [see also: 15]. We hypothesised that compared to the TC and HC groups, patients with cPTSD exhibit increased interference for trauma-related words as reflected in overall slower reaction times and more errors in the CEST as well as in the memory tasks. We also expected increased neural activity during emotional (especially trauma-related) words in the amygdala, insula and dACC, as well as decreased activation in the dlPFC and vmPFC.

Materials and methods

Participants

The sample consisted of 28 women with cPTSD and 28 female TCs, with both groups having experienced childhood sexual or physical abuse and 28 female HCs, matched for age and education. Clinical diagnoses and childhood abuse in patients with cPTSD and the TC group were assessed retrospectively by trained diagnosticians using the Structure Clinical Interview for DSM-IV Axis I Disorders [SCID-I; 31], the Clinician Administered PTSD Scale [CAPS; 32] and the borderline personality disorder (BPD) section of the International Personality Disorder Examination [IPDE; 33]. Patients with cPTSD had to fulfill the DSM-5 criteria for PTSD after sexual or physical abuse before the age of 18. Because patients with cPTSD who participated in the current study were recruited from a larger randomised controlled trial (RCT), comparing two different outpatient psychological treatments for cPTSD and co-occurring BPD-features, enrolment was restricted to women aged 18–65 who additionally had to fulfill at least three criteria of BPD (including the criterion affective instability) as defined by the IPDE, as we aimed to include highly impaired patients with cPTSD. TC and HC groups were recruited via advertisements in local newspapers, internet and flyers. Inclusion criteria for the TC group were sexual or physical abuse before the age of 18. Exclusion criteria for the TC and HC groups were any current or previous mental disorder, any psychotherapeutic experience or any intake of psychotropic medication [for more detailed descriptions of the TC sample see: 34]. General exclusion criteria were traumatic brain injuries, current and lifetime schizophrenia or bipolar-I disorder, mental retardation, severe psychopathology or somatic illness that needs to be treated immediately in another setting (e.g., BMI <16), medical conditions making exposure-based treatment impossible, a suicide attempt within the past 2 months and substance dependency with no abstinence within 2 months prior to the study. For the current fMRI study, further exclusion criteria were metal implants, pregnancy, left-handedness and claustrophobia. Self-report measures included retrospective questionnaires on childhood trauma (Childhood Trauma Questionnaire; [CTQ; 35]), PTSD symptomatology (Davidson Trauma Scale; [DTS; 36]), and the severity of depressive mood (Beck Depression Inventory; [BDI-II; 37]). The study was approved by the Ethical Board II of Heidelberg University, Germany, and was conducted according to the Declaration of Helsinki at the Central Institute of Mental Health in Mannheim. Written informed consent was obtained from the participants after the procedures had been fully explained. All subjects received monetary remuneration for participation in the study.

As expected, patients with cPTSD scored higher than the TC and HC groups in all clinical variables (CTQ, DTS and BDI-II). Details on demographic data and clinical characteristics of the sample are reported in Table 1.

Classic and emotional Stroop tasks

The CEST consisted of 80 randomised blocks of four words each (total 320 words), differing in word category and presented in a block-design: 20 trauma-related words (e.g., 'abuse'), 20 general negative words (e.g., 'cry'), 20 neutral words (e.g., 'shape') and four colour words in congruent (e.g., 'red' written in red) as well as incongruent conditions (e.g., 'red' written in blue). Neutral words were used as baseline condition (control task). The words used in the EST were derived from a pilot study conducted with seven researchers with expertise in PTSD from our group as well as seven patients with childhood abuse-related complex PTSD (for further details see supplement S1). Each colour was assigned to a button, which participants were able to press with their right index, middle, ring, or little finger. Each word was presented four times (once in each of the four colours) for 1500 ms. Participants were asked to press the button that corresponds to the colour in which the word is printed within this period. Inter-trial intervals between two words were jittered, with a mean of 300 ms. For timing efficiency, baseline-intervals (i.e., a fixation cross) between two task blocks were optimised with optseq 2 (http://surfer.nmr.mgh.harvard.edu/optseq), with a mean of 798.77 ms. Before the task began, colour naming was trained in 20 trials with non-word stimuli (e.g., 'XXX' written in red). Immediately after the CEST, participants were asked to report all the words they remembered from the CEST in a spontaneous free recall task. Subsequently, the 60 previous words of the EST and 60 new words comparable in valence, arousal, word length and frequency were presented randomly for an old/new-recognition task. After scanning, participants rated all words of the EST regarding valence and arousal on a five-point Likert scale by the self-assessment manikin scale [SAM; 38] (see supplement S2 for ratings).

MRI scan protocol

Scanning was conducted on a Siemens 3 Tesla TRIO-Scanner (Siemens Medical Solutions, Erlangen, Germany). Using three-dimensional magnetisation-prepared rapid-acquisition gradient echo (MPRAGE; T1-weighted contrast, voxel size $1 \times 1 \times 1$ mm^3), a high-resolution anatomical scan was acquired for each participant as an individual template for the functional data. The blood oxygen level-dependent signal was measured with 36 transversal slices (3 mm, descending) covering the entire brain using gradient-echo, echo-planar imaging [EPI, T2-weighted contrast, field of view = 192×192 mm, voxel size $3 \times 3 \times 3$ mm^3, 64×64 voxel matrix, flip angle 80°, echo time (TE) = 30 ms, repetition time (TR) = 2000 ms]. The first five scans were discarded to minimise T1 effects. Head movement artefacts and scanning noise were restricted using head cushions and headphones.

Statistical analyses

Behavioural data

Reaction times (RTs; in ms) were log-transformed (base10) due to non-normality to minimise the effect of outliers [for review see: 39]. All statistical analyses were conducted for correctly answered trials only (M = 97% of all trials, SD = 5.17%). Task performance (accuracy and RTs) for the CEST as well as memory function (free recall and

Table 1 Demographic and clinical variables in patients with complex post-traumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects

	cPTSD ($n = 28$)		TC ($n = 28$)		HC ($n = 28$)		Statistics		Post-hoc t tests
	M	(±SD)	*M*	(±SD)	*M*	(±SD)	*F*	*p*	
Age (years)	30.61	(9.99)	30.21	(12.11)	30.50	(7.98)	0.011	0.99	
CTQ (total score)	75.88	(20.10)	51.21	(13.09)	31.18	(6.76)	67.65	0.001	HC < TC < cPTSD
CTQ (physical abuse)	11.5	(5.41)	9.36	(4.0)	5.64	(1.81)	15.23	0.001	HC < TC n.s. cPTSD
CTQ (sexual abuse)	15.0	(6.68)	10.63	(5.59)	5.07	(0.23)	27.42	0.001	HC < TC < cPTSD
DTS (frequency)	38.03	(10.99)	7.37	(7.30)	–	–	147.74	0.001	TC < cPTSD
Severity	41.89	(11.86)	6.78	(9.24)	–	–	148.33	0.001	TC < cPTSD
BDI (II–total score)	35.39	(11.12)	3.30	(4.12)	3.39	(3.87)	184.86	0.001	HC n.s. TC < cPTSD
Years of education, *n* (%)									
9 years	1	(3.57)	0	(0)	1	(3.57)	0.50	0.61	
10 years	11	(39.29)	9	(32.14)	8	(28.57)			
12 years	16	(57.14)	19	(67.86)	19	(67.86)			
Co-morbidities, *n* (%)									
BPD	17	(60.70)							
Major depressive disorder	16	(57.10)							
Social phobia	9	(32.10)							
Specific phobia	5	(17.90)							
Panic disorder	5	(17.90)							
Obsessive compulsive disorder	5	(17.90)							
Bulimia nervosa	4	(14.30)							
Binge eating disorder	3	(10.70)							
Generalised anxiety disorder	2	(7.10)							
Somatization disorder	1	(3.60)							
Psychotropic medication, *n* (%)									
Unmedicated	9	(32)							
SSRI/SNRI	13	(46)							
Other antidepressants	6	(21)							
Neuroleptics	8	(28)							
Anticonvulsants	3	(11)							

cPTSD complex post-traumatic stress disorder, *TC* trauma-exposed healthy subjects, *HC* non-trauma exposed healthy subjects, *BPD* Borderline Personality Disorder, *CTQ* Childhood Trauma Questionnaire, *DTS* Davidson Trauma Scale, *BDI-II* Beck Depression Inventory II, *M* mean, *SD* standard deviation, Post-hoc *t* tests were performed at a significance level of $p < 0.05$ Bonferroni-corrected, *ns* not significant at a significance level of $p < 0.05$

recognition task) was analysed via repeated measure analysis of variance (rm-ANOVAs), including the within-subject factor condition (negative minus neutral, trauma minus neutral and colour minus neutral; for the free recall and recognition task: negative minus neutral and trauma minus neutral) and the between-subject factor group (cPTSD, TC, or HC). Post-hoc data analyses were run in order to control for the influence of early childhood traumatization and years of education on main findings. In case of significant effects for the dependent variables, post hoc Bonferroni-corrected t tests and effect sizes (partial eta-squared [η_p^2], Cohen's d [40]) were computed. All behavioural analyses were performed with IBM SPSS Statistics 23 (IBM, USA), assuming a statistical significance level of $p < 0.05$, using Greenhouse–Geisser correction when necessary.

fMRI data

Functional imaging data were analysed using standard procedures implemented in Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). The EPI time series were pre-processed according to usual practice: slice time correction, spatial realignment to the mean image to correct for head motion, coregistration onto participants' segmented high-resolution T1 scan, normalisation to the standard brain of the Montreal Neurological Institute (MNI) space and smoothing with a Gaussian kernel with full-width at half maximum of 6 mm. We did not have to exclude subjects due to excessive head motion. To control for potential artefacts, scan-to-scan movements and changes in global signal intensity were screened using the ART software package (http://www.nitrc.org/projects/artifact_detect). Movement was specified based on the six parameters received from the realignment step. Movements greater than 2 mm and global signal intensity changes of $z > 9$ were classified as outliers. Nuisance regressors controlling for outlier scans were introduced with the six movement regressors included as nuisance variables in the first-level models. First-level analyses were set up according to the respective experimental conditions (with negative, trauma, colour and neutral word blocks as regressors of interest), and button presses as well as movement parameters as regressors of no interest. We defined the following contrasts at the subject level: (1) negative > neutral, (2) trauma > neutral and (3) colour > neutral.

Whole-brain voxel-wise analysis

Data analyses at group level involved both a whole-brain voxel-wise analysis and region-of-interest (ROI) analyses to evaluate group differences during different conditions. A full factorial model (three groups × three conditions) was used including the *F* contrast 'main effect of group' (cPTSD, TC and HC), 'main effect of condition' (negative > neutral, trauma > neutral and colour > neutral) and 'interaction effect group × condition'. A statistical threshold of $p < 0.05$, family-wise error (FWE) corrected was applied.

Region of interest analysis

In line with the neurocircuit model of PTSD and our hypotheses, we specifically hypothesised effects of emotional stimuli on limbic (amygdala, insula) and prefrontal (dlPFC, vmPFC, dACC) brain regions. Accordingly, we used anatomical masks (left and right hemisphere separately) as defined by the Automated Anatomical Labeling software [41], smoothed with a cube of voxels of size (FWHM) 9 mm. Since our aim was to investigate posterior and anterior parts of the insula separately, anatomical masks of the insula provided by the Harvard–Oxford cortical and subcortical structural atlases [42] were split at $y = 0$ in anterior and posterior parts. All analyses were conducted with a threshold of $p_{(\mathrm{FWE})} < 0.05$. In case of significant differences, two-tailed post hoc Bonferroni-corrected *t* tests ($p < 0.05$) were performed using SPSS after extracting beta values of the respective peak voxel, and effect sizes (η_p^2) were computed. To check for confounding effects of CTQ score, differences in RTs as well as correct reactions on brain activation, we correlated beta values of the peak voxels with CTQ score, differences in RTs and correct reactions.

Results

Behavioural results

Classic and emotional Stroop task performance

Descriptive statistics for behavioural CEST performance are summarised in Table 2. For interference scores regarding RTs, we found a significant main effect for condition ($F_{1.81,146.57} = 28.60$, $p < 0.001$, $\eta_p^2 = 0.26$), a significant interaction between group and condition ($F_{3.62,146.57} = 6.42$, $p < 0.001$, $\eta_p^2 = 0.14$) as well as a trend for a group effect ($F_{2,81} = 2.69$, $p = 0.07$, $\eta_p^2 = 0.06$). Post-hoc *t* tests revealed significant differences between cPTSD and TC/HC groups in the trauma condition (cPTSD vs TC: $t_{44.14} = 2.45$, $p < 0.05$, $d = 0.68$; cPTSD vs HC: $t_{34.38} = 4.06$, $p < 0.001$, $d = 1.19$) (Fig. 1a). There were no significant group differences between the TC and HC groups in any condition. Regarding accuracy scores, we found a significant main effect of group ($F_{2,81} = 4.63$, $p < 0.05$, $\eta_p^2 = 0.10$), condition ($F_{2,162} = 3.54$, $p < 0.05$, $\eta_p^2 = 0.04$) as well as a significant interaction of group and condition ($F_{4,162} = 2.97$, $p < 0.05$, $\eta_p^2 = 0.07$) (Fig. 1b). Post-hoc *t* tests revealed significant differences between cPTSD and TC/HC groups in the trauma condition (cPTSD vs TC: $t_{27.93} = -2.21$, $p < 0.05$, $d = -0.75$; cPTSD vs HC: $t_{27.93} = -2.15$, $p < 0.05$, $d = -0.72$). Moreover, post hoc *t* tests revealed a statistical trend between cPTSD patients and the TC group in the colour condition (cPTSD vs TC: $t_{28.63} = -1.89$, $p = 0.07$, $d = -0.62$). There were no significant differences between the TC and HC groups in any condition (see supplement S3 and S4 for detailed analyses). Stroop interference regarding RT and accuracy did not correlate with CTQ score. When controlling for years of education, interaction effects and main effects remained significant.

Free recall and recognition tasks

We observed a significant main effect for condition in the recall ($F_{1,81} = 177.29$, $p < 0.001$, $\eta_p^2 = 0.69$) as well as in the recognition task ($F_{1,81} = 99.86$, $p < 0.001$, $\eta_p^2 = 0.55$), but no significant group difference or interaction effect between condition and group. Trauma-related words were remembered and recognised better across all groups. CTQ score and years of education did not correlate with memory functions in both tasks.

fMRI results

Whole-brain voxel-wise analysis

In all groups, the CEST activated similar brain areas as in prior Stroop tasks, that is, dlPFC, right amygdala,

Table 2 Behavioural data of the classic and emotional Stroop task and related memory tasks in patients with complex post-traumatic stress disorder, trauma-exposed healthy subjects and non-trauma exposed healthy subjects, absolute values per word category

	Descriptive data					
	CPTSD (*n* = 28)		TC (*n* = 28)		HC (*n* = 28)	
	M	(±SD)	M	(±SD)	M	(±SD)
Stroop task						
Reaction times (ms)						
Negative words	771.56	(161.32)	661.73	(92.83)	652.42	(94.97)
Trauma-related words	854.74	(229.50)	680.75	(96.99)	664.09	(97.94)
Neutral words	750.69	(151.60)	640.79	(81.61)	645.21	(99.31)
Colour words	818.58	(188.20)	699.93	(88.46)	714.42	(128.19)
Accuracy (%correct)						
Negative words	97.56	(2.93)	98.36	(2.63)	98.32	(1.96)
Trauma-related words	90.60	(17.67)	98.72	(1.81)	98.14	(2.79)
Neutral words	97.84	(2.34)	98.72	(1.53)	98.35	(2.41)
Colour words	92.16	(14.99)	98.14	(2.34)	97.08	(4.41)
Free recall (*n*)						
Negative words	1.54	(2.34)	1.64	(1.57)	1.61	(1.71)
Trauma-related words	5.00	(2.51)	4.71	(2.03)	4.25	(2.68)
Neutral words	0.75	(1.04)	1.29	(1.44)	1.39	(1.81)
Recognition task						
Accuracy (%correct)						
Negative words	30.75	(4.48)	30.07	(2.84)	28.93	(3.69)
Trauma-related words	34.21	(3.04)	34.36	(2.61)	32.61	(3.18)
Neutral words	29.82	(5.73)	29.96	(3.42)	28.89	(4.40)

cPTSD complex post-traumatic stress disorder, *TC* trauma-exposed healthy subjects, *HC* non-trauma exposed healthy subjects, *M* mean, *SD* standard deviation, reaction times were log-transformed for analyses and refer to correct responses

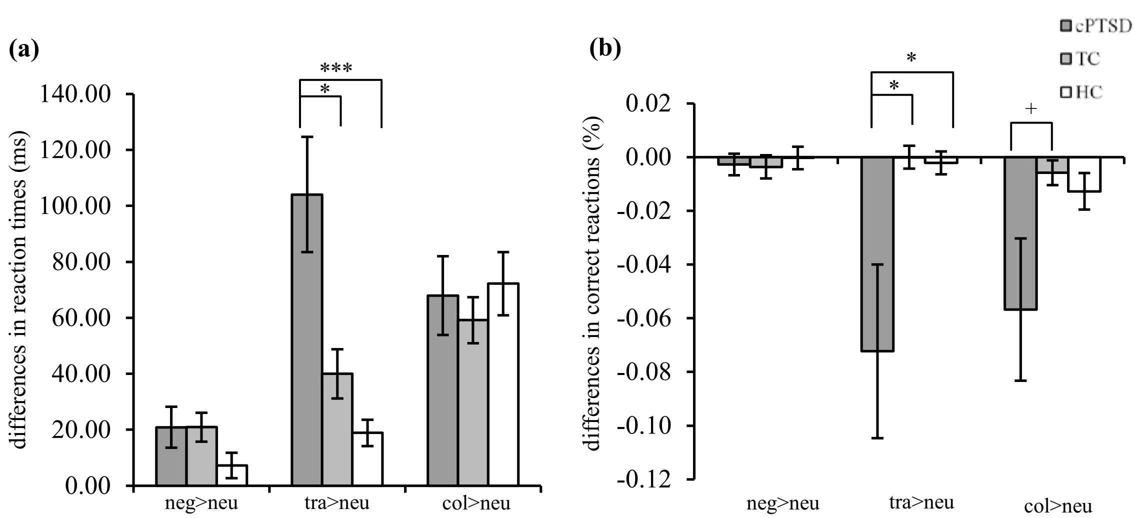

Fig. 1 Means ± standard error of the mean (SEM) of differences of reaction times (ms) (**a**) and of differences of correct reactions (%) (**b**) in patients with complex post-traumatic stress disorder (cPTSD), trauma-exposed healthy subjects (TC) and non-trauma exposed healthy subjects (HC). *Lines* and *asterisks above bars* on *bar* graph indicate significant differences of post hoc *t* tests amongst groups during the experimental conditions. Neg > neu: negativ words minus neutral words, tra > neu: trauma-related words minus neutral words, col > neu: colour words minus neutral words. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{+}p < 0.09$

orbitofrontal cortex, superior temporal gyrus, inferior parietal lobe and occipitotemporal regions (for complete description of suprathreshold clusters of the main effect condition see supplement S5). At the whole brain level, we did not observe any clusters that survived FWE-correction for the *F* contrast group and the interaction group × condition.

ROI analysis

The ROI analyses revealed a significant interaction (group × condition) for the right dlPFC, left vmPFC, right dACC and a trend for the left dACC and right anterior insula, but not in posterior insula and amygdala (see Table 3 for further details and Fig. 2 for significant clusters). In case of significant interaction effects, post hoc Bonferroni-corrected *t* tests between groups were calculated for each condition (see below). Brain activation did not correlate with CTQ score, differences in RTs or correct reactions.

dlPFC Means and standard error of the mean of percentage signal change in the right dlPFC are displayed in Fig. 2a. Post-hoc *t* tests revealed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the TC ($t_{54} = 2.48$, $p < 0.05$, $d = 0.67$) and HC ($t_{54} = 3.17$, $p < 0.001$, $d = 0.85$) groups.

vmPFC Means and standard error of the mean of percentage signal change in the left vmpfc are depicted in Fig. 2b. Post-hoc *t* tests revealed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the TC ($t_{54} = 2.53$, $p < 0.05$, $d = 0.68$) and HC ($t_{41.30} = 3.93$, $p < 0.001$, $d = 1.10$) groups.

dACC Means and standard error of the mean of percentage signal change in the right and left dACC are depicted in Fig. 2c, d. Post-hoc *t* tests revealed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the TC (right dACC: $t_{54} = 2.27$, $p < 0.05$, $d = 0.61$; left dACC: $t_{43.53} = 2.73$, $p < 0.05$, $d = 0.75$) and HC (right dACC: $t_{40.72} = 3.30$, $p < 0.001$, $d = 0.92$; left dACC: $t_{40.99} = 3.41$, $p < 0.001$, $d = 0.95$) groups.

Insula Means and standard error of the mean of percentage signal change in the right anterior insula are displayed in Fig. 2e. Post-hoc *t* tests showed significantly higher activation during the presentation of trauma-related words in cPTSD patients compared to the HC group ($t_{54} = 4.54$, $p < 0.001$, $d = 1.23$). Post-hoc comparisons between TC and cPTSD or rather TC and HC groups revealed no significant differences.

Discussion

The goal of the present study was to examine changes in brain activity in patients with childhood abuse-related cPTSD and TC and HC groups. Increased Stroop interference in cPTSD patients, as marked by slower RTs and more errors, was significantly increased for trauma-related words compared to both control groups. Thus, the present data suggest a specific attentional bias and greater interference in patients with cPTSD towards trauma-related stimuli. This has been shown repeatedly

Table 3 Statistic results of region of interest analyses, two-way interaction effect (group × condition)

Location			Statistics				Coordinates (MNI)		
BA	Hemisphere R/L	Anatomical lable	Cluster	*Z*	*P*FWE (SVC)	η_p^2	*X*	*Y*	*Z*
9	R	Superior frontal gyrus	166	3.94	0.01*	0.15	36	47	31
9	L	Superior frontal gyrus	61	3.16	0.22	0.13	−39	29	37
10	R	Middle frontal gyrus	70	2.83	0.21	0.10	39	56	−2
10	L	Middle frontal gyrus	44	4.40	<0.001***	0.16	−36	59	−2
32	R	Cingulate gyrus	89	3.37	0.01*	0.14	6	23	40
32	L	Cingulate gyrus	106	3.36	0.05^{+}	0.12	−3	20	37
13	R	Anterior insula	284	3.36	0.08^{+}	0.12	45	11	1
13	L	Anterior insula	185	2.42	0.62	0.08	−45	17	1
13	R	Posterior insula	24	3.03	0.18	0.10	27	17	−11
13	L	Posterior insula	1	1.45	0.94	0.06	−39	−10	19
*	R	Amygdala	8	2.00	0.37	0.06	18	2	−20
*	L	Amygdala	6	2.36	0.22	0.07	−30	2	−17

FWE family-wise error corrected, *p* (FWE) <0.05, *k* >10 voxel, *BA* Brodmann Area

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, $^{+}$ $p < 0.09$

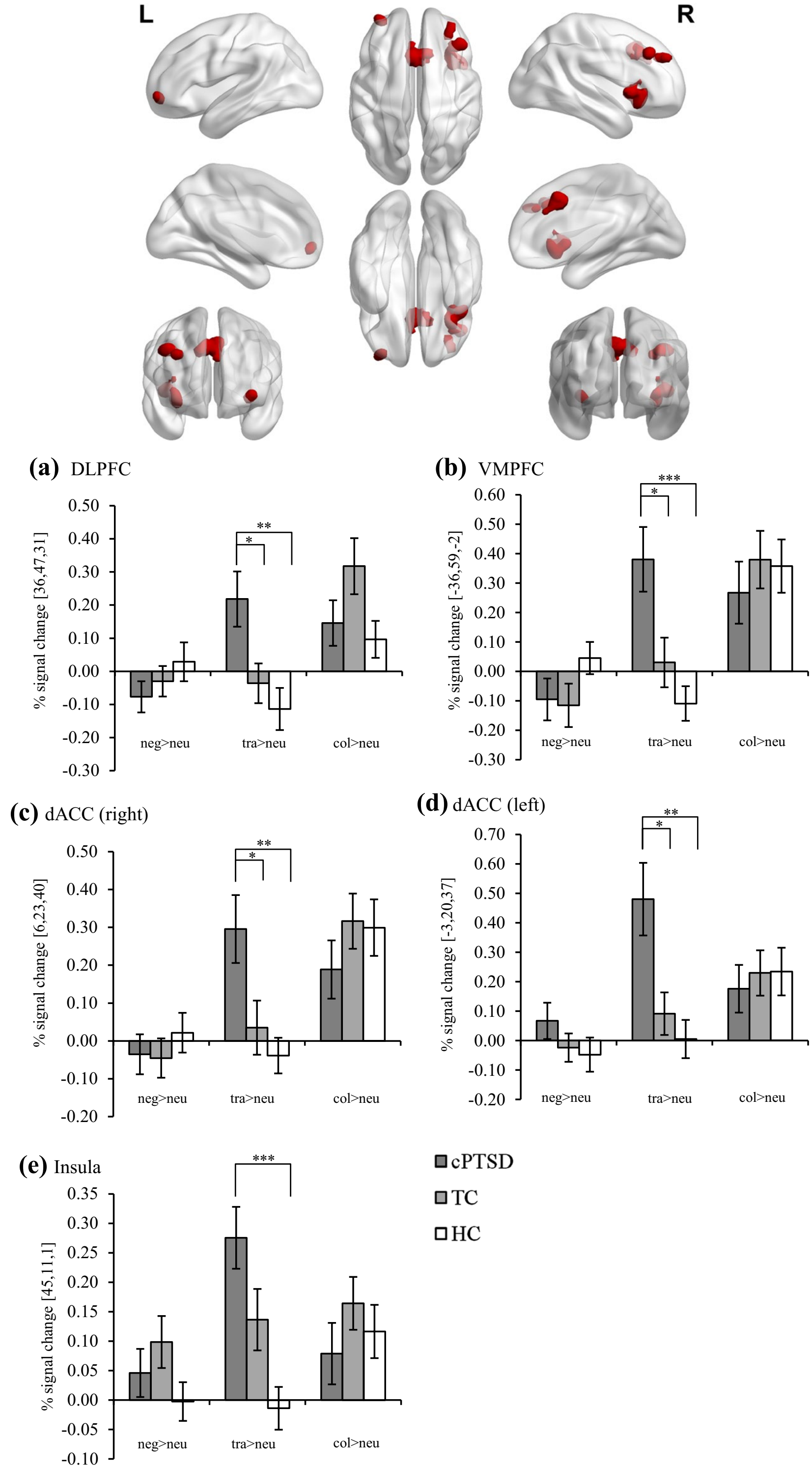

Fig. 2 Results of the region of interest (ROI) analyses: Significant clusters in the two-way interaction effect (group × condition) and percentage signal change during the experimental conditions (neg > neu, tra > neu, col > neu) for (**a**) the dorsolateral prefrontal cortex (DLPFC; [31, 36, 47]), (**b**) ventromedial prefrontal cortex (VMPFwords minus neutralC; [−36, 59, −2]), (**c**) right dorsal anterior cingulate cortex (dACC; [6, 23, 40]), (**d**) left dorsal anterior cingulate cortex (dACC; [−3, 20, 37]) and (**e**) insula [1, 11, 45] in patients with complex post-traumatic stress disorder (cPTSD), trauma-exposed healthy subjects (TC) and non-trauma exposed healthy subjects (HC). *Error bars* represent standard error of the mean (SEM). *Lines* and *asterisks* above *bars* on *bar* graph indicate significant differences of post hoc *t* tests amongst groups during the experimental conditions. Neg > neu: negativ words minus neutral words, tra > neu: trauma-related words minus neutral words, col > neu: colour words minus neutral words. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{+}p < 0.09$

in patients with PTSD [e.g., 11] which is in line with the symptoms of hyperarousal, intrusions and enhanced attention to threatening stimuli. Moreover, in the context of trauma-related words, patients with cPTSD showed increased activation in the dlPFC, vmPFC and dACC compared to both control groups and a trend for increased activation in the right anterior insula compared to the HC group.

In line with our hypotheses, patients with cPTSD showed increased dACC activation during trauma-related stimuli compared to both control groups. The literature contains supporting data regarding activation of dACC in PTSD patients, with higher dACC activation found using CST [15], EST [30], counting Stroop [43] and affective Stroop [21]. The dACC has been shown to be reliably activated in interference paradigms such as the Stroop task [44]. Higher dACC activation in our cPTSD sample may reflect greater response conflicts and might increase cognitive resources in the trauma condition vs other conditions [43]. The dACC is also discussed to be part of the salience network, which may play a role in hypervigilance in PTSD. Therefore, higher dACC activation might reflect a state of high arousal and attention in cPTSD that is specifically caused by trauma-related information [45]. Bush et al. [46] demonstrated that significant activation in dACC was related to response time increases across conditions. Yet in our study, activation of this region was not accompanied by significant response time increases in cPTSD patients.

As expected, patients with cPTSD revealed a trend for increased activation in the anterior insula compared to the HC group when presented with trauma-related words. These results are in line with several previous studies, suggesting increased activation in the insula in PTSD patients when presented with trauma [47], negative [48] and non-emotional cues [15]. However, another study using the EST found decreased posterior insula activation [30].

Several studies have shed light on differences between functional circuits associated with the anterior and posterior insula. As extensively reviewed, the anterior and posterior insular cortices have different patterns of connectivity with other brain regions [49]. Results suggest an important role for the anterior insula with regard to cognitive control, salience detection and attentional processes [50]. It is discussed as an integral hub mediating information flow across brain networks that are involved in attentional processing and cognition, whereas more sensory attributes and interoception are thought to be represented in posterior insula [49, 51]. In this case, hyperactivity of the anterior insula might be related to pathologically enhanced salience detection [49]. Moreover, previous work provides evidence that the right anterior insula is among others involved in response inhibition of a prepotent behaviour in case of response-conflict tasks [52]. Therefore, our finding of increased anterior insula activation may point either to higher arousal in patients with cPTSD in response to trauma-related stimuli, or to a greater response-conflict in case of trauma-related stimuli. The latter would also be in line with activation of the anterior insula in all groups during the colour condition. Possibly, our study design was suited to elicit effects in the anterior insula, but not in the posterior insula. Future studies might further investigate differences between functional circuits of the anterior and posterior parts of the insula in cPTSD. The TC group did not differ significantly from patients with cPTSD or from the HC group. This is not in line with Lindauer and colleagues [53] demonstrating greater insula activation during script-driven imagery in PTSD patients compared to a TC group. One may explain this divergent finding with sample characteristics (cPTSD vs single-trauma) or different paradigms (Stroop vs script-driven imagery).

Contrary to our hypothesis, we did not find higher amygdala activity in response to trauma-related words compared to neutral words in patients with cPTSD as observed in previous studies [21, 22, 54]. Some recent studies have also failed to find alterations in amygdala activity in PTSD patients in response to trauma-related cues [15, 55, 56]. One possibility relates to the contextual demands of the CEST which may not have been optimally suited to elicit effects in the amygdala, but rather engaged prefrontal regions that subserve functions of cognitive control (dlPFC, vmPFC, dACC). Moreover, previous meta-analyses of functional neuroimaging studies on emotion processing in depression [57] and BPD [58] showed dampening effects of medication on amygdala activity. Several studies have also reported attenuated amygdala activation corresponding with increased dlPFC activity [55, 59]. These results are supported by a meta-analysis, showing attenuated amygdala activity in the context of increasing attentional demands [60].

Our findings differ from previous fMRI studies that have typically found decreased activation in the dorsal, lateral and ventral PFC regions [25, 45]. The current results point to greater dlPFC and vmPFC engagement in cPTSD patients during trauma-related words compared to both control groups. However, more recent studies have been consistent with our results with greater dlPFC [21, 55] and vmPFC [48, 61] activation. Fonzo and colleagues [55] found greater dlPFC activation in response to negative stimuli in PTSD patients after childhood maltreatment compared to PTSD patients with no childhood maltreatment history. In a sample of sub-threshold military patients with PTSD symptoms, White et al. [21] showed increased interference and increased activation in the dorsal lateral regions in response to emotional (relative to neutral) stimuli in participants with greater symptom severity. We suggest that increased dlPFC response in our cPTSD sample relates to task demands specific for CEST. It is most likely that trauma-related words in the context of this cognitive paradigm were distressing to patients with cPTSD. The aim of responding as quickly as possible to the correct colour while being confronted with trauma-related words may have activated cognitive control networks. Therefore, increased dlPFC activation might reflect higher expenses of cognitive control resources to trauma-related cues in cPTSD patients compared to TC and HC groups, or may be a compensatory mechanism to correct for enhanced attentional threat orientation to task-relevant demands [62].

Contrary to our hypothesis, we found greater vmPFC activation in cPTSD patients during trauma-related words compared to both control groups. However, as many studies also found hyperactivation in vmPFC regions, this result is convergent with some previous studies. In a sample of Iraq war veterans, Morey and colleagues [63] showed hyperactivity in the vmPFC in PTSD patients during processing of trauma-related vs trauma-unrelated material. Further studies demonstrated hyperactivation within vmPFC regions in PTSD patients during an auditory oddball paradigm [64], response-inhibition task [65] and script driven imagery of childhood trauma [66]. It is important to note that the vmPFC subserves different functions of both inhibition (successful suppression of emotional responses to a negative emotional signal), or rather emotion regulation and facilitation of autonomic arousal [45, 67]. Thus, our findings may reflect increased effort in the trauma vs other conditions in the cPTSD group as well as regulation of autonomic arousal during the cognitive task.

In order to differentiate between the long-lasting effects of childhood abuse and consequences of cPTSD, we included a TC control group. On the behavioural level as well as on the neural level (except for the anterior insula), the TC group revealed significant differences to the cPTSD group, but no significant differences compared to the HC group in any condition. These results are in line with Cisler et al. [17] who also did not find any attention bias towards trauma-related words in the TC group. The current fMRI data are not in line with another study, showing superior recruitment of regions implicated in cognitive control in a TC group compared to patients with PTSD and a HC group [22]. The current results suggest that the attentional bias to trauma-related stimuli and corresponding alterations in prefrontal brain regions are related to cPTSD and not to trauma exposure itself. One could speculate that the TC group was not distracted by the trauma-related stimuli, which in turn could be a crucial resilience factor that could prevent the development of cPTSD [7].

Patients with cPTSD showed neither impairments nor advantages in memory functions for threat information, as examined in the free recall and recognition tasks. This is in line with Stein et al. [20] who found no differences in patients with PTSD in an explicit memory task. The data are not in line with studies demonstrating evidence for a memory advantage in patients with PTSD vs TC/HC groups for threat information [19, 68]. These studies suggest that patients with cPTSD do not exhibit impaired encoding and memory for traumatic information.

While the present study had a number of strengths, including a representative cPTSD group sample after childhood abuse, a TC and HC group sample (matched regarding age and education), several limitations are worth noting. First, the inevitable use of psychotropic medication in our cPTSD sample has to be considered. While some studies did not find any influence of psychotropic medication on cognitive and psychomotor performance [69] as well as emotion processing and brain activity [70], other studies point to significant influences on cognitive performance and emotion processing caused by differences in pharmacological profiles [71, 72]. Therefore, we cannot rule out that medication effects might have confounded our results. To clarify the role of medication on cognitive performance and emotion processing in cPTSD, future studies would need to recruit drug-naive cPTSD patients. Second, the majority of our cPTSD sample had a high rate of comorbid BPD, major depression and social anxiety. Given that cPTSD after childhood abuse is associated with high co-occurring symptoms of depression, interpersonal problems and anxiety as well as personality disorders [73, 74], our sample is representative for this group of patients. However, it could be argued that these comorbid disorders (especially BPD and major depression), rather than cPTSD, accounted for the observed results. Thus, future research might study cPTSD patients, BPD, major depression and social anxiety disorders separately to strengthen the internal validity of the psychobiology of PTSD. However, this would come at the expense of external validity, as the syndrome of cPTSD is defined by symptoms and comorbidity with the respective disorders. Moreover, we only included female patients. Consequently, the results of our study are restricted to a female sample of cPTSD patients and cannot be generalised to male patients, who might show other reactions to trauma-related cues. However, most studies on PTSD in the general population have found higher rates of PTSD in women than in men (esp. after childhood interpersonal violence) [75, 76], and men are less likely to seek psychotherapy [77]. Moreover, fMRI studies have also reported gender-related differences in terms of BOLD activation in prefrontal and limbic regions during emotional and cognitive tasks, and it is, therefore, useful to include a homogenous sample of either women or man [78]. Third, we used congruent and incongruent colour words as one condition in the CST. As a consequence, we were not able to analyse the CST separately. Fourth, although groups were matched for demographic parameters and age, patients with cPTSD reported more severe traumatic experiences compared to the TC group, as measured with the CTQ. However, post hoc analyses suggest no significant association of our results with cPTSD patients' trauma experience as measured by CTQ. Finally, it has to be noticed that our statistics are limited by low statistical power, which might have caused false negative results. With the given sample of $n = 84$, $\alpha = 0.05$ and $\beta = 0.05$, 3 between-subject factors and 3 within-subject factors, a sensitivity power analysis conducted with G*Power [79] indicated that the smallest interaction effect that can be ruled out is Cohen's $f = 0.34$. This means that we cannot rule out medium or small effects ($f = 0.25$ or less) [according to 40] with sufficient certainty, given the sample size.

Taken together, our results are not completely in line with the hypothesised neurocircuitry model of PTSD. We could replicate increased dACC and a trend for increased insula activation during trauma-related stimuli in cPTSD patients, but did not find increased amygdala activation. Moreover, we found greater dlPFC and vmPFC activation in the presence of trauma-related words. Greater activation in these brain regions, which subserve inhibition of distracting stimuli, attentional control and emotion regulation, together with no significant group differences in the amygdala may reflect the cognitive demands of the Stroop task and may point to efforts to compensate for emotional distraction caused by the trauma-related words in cPTSD [80].

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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