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History of childhood maltreatment augments dorsolateral prefrontal processing of emotional valence in PTSD

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ABSTRACT

Posttraumatic stress disorder (PTSD) is characterized by conflicting findings of both increased and decreased amygdala and prefrontal reactivity to threat or trauma stimuli. Childhood maltreatment (CM), a potent risk factor for PTSD, exerts long-lasting influences on threat processing and prefrontal-amygdala function. This suggests that CM history may influence PTSD neural phenotypes related to threat processing. Here, we adapt a well-characterized emotional conflict paradigm to investigate CM effects on both emotional conflict and emotional valence processing within PTSD stratified by task relevance. Forty-two individuals with PTSD (22 reporting extensive CM history (PTSD-CM)) and 20 trauma-exposed healthy controls (TEHCs) underwent functional magnetic resonance imaging while identifying affect of emotional faces (fear and happy) overlaid with a goal-irrelevant emotional distractor word ("FEAR" or "HAPPY"). We examined effects of CM on conflict, conflict adaptation, valence-related activation (fear vs. happy) for goal-relevant (face) and goal-irrelevant stimuli (word), and valence effects in interaction with goal-relevancy (face vs. word). Though no activation differences between groups were observed for conflict contrasts nor for valence effects in the amygdala, CM status interacted with valence processing differences as a function of goal relevance in the left dorsolateral prefrontal cortex (dlPFC). Here, PTSD-CM displayed greater activation relative to PTSD to negative valence when stimuli were goal-irrelevant. CM history also moderated relationships between activation abnormalities and PTSD re-experiencing symptoms. These findings provide initial evidence that CM history augments dorsolateral prefrontal bias to implicitly processed stimulus valence in PTSD.

1. Introduction

Increased attention to negative valence emotional stimuli signaling a potential threat, i.e. a threat-related attention bias, is a consistently demonstrated characteristic of anxiety disorders (Bar-Haim et al., 2007). However, research in posttraumatic stress disorder (PTSD) has demonstrated inconsistent results characterized by attention bias both towards (Bar-Haim et al., 2007) and away from threat (Bar-Haim et al., 2010), consistent with an exaggerated attention bias variability (Naim et al., 2015). PTSD is also characterized by conflicting findings with respect to amygdala activation, wherein both increased and decreased activation to threat and trauma-related stimuli has been observed in patients (Etkin and Wager, 2007). In combination with the established role of the amygdala in threat detection and responsivity (Costafreda et al., 2008), this variability in amygdala reactivity in PTSD suggests that neural abnormalities in threat processing may be affected by attentional mechanisms governing task relevance and goal-oriented behavior.

A recent meta-analysis of amygdala activation to emotional stimuli demonstrated that amygdala reactivity is heightened during implicit/passive stimulus processing relative to explicit/active conditions, i.e. when processing of the emotional stimulus is incidental and not the focus of task-relevant goals and behavior

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(Costafreda et al., 2008). This difference in amygdala reactivity as a function of attentional processing may arise as a consequence of increased medial and lateral prefrontal engagement with greater depth of conscious processing, which serves to downregulate amygdala responses (Taylor et al., 2006). Thus, variability in prefrontal-amygdala interactions relating to processing depth of emotional stimuli could explain variability in observed PTSD neural abnormalities. Moreover, recent research suggests that different prefrontal regions modulate different aspects of bottom-up reactivity instantiated in the amygdala. Whereas the medial prefrontal cortex is involved with bottom-up appraisal of stimulus valence, the dorsolateral prefrontal cortex (dlPFC) serves to augment threat or valence-related attentional processes (Comte et al., 2016), which is consistent with the proposed role of the dlPFC in regulating amygdalar emotional reactivity (Delgado et al., 2008; Ray and Zald, 2012) and observations for indirect amygdalar-dlPFC connections (Eden et al., 2015).

The clinical syndrome of PTSD also often comes in the context of major stressors experienced prior to the onset of the disorder-inducing traumatic event. Childhood maltreatment, a particularly damaging form of early life stress, has been described as a robust risk factor for PTSD (Zlotnick et al., 2008) as well as for the adult onset of mood and anxiety disorders (Green et al., 2010). Moreover, early life stress has been shown to impact amygdala-prefrontal structure and function (De Bellis and Keshavan, 2003; Fonzo et al., 2013; Gatt et al., 2010; Miller et al., 2015; Taylor et al., 2006; Tottenham et al., 2011, 2010), suggesting that childhood maltreatment may serve as an important determinant of amygdala-prefrontal responses to threat-conveying stimuli within PTSD. Other recent studies have found that altered amygdala and prefrontal responses as a function of maltreatment history can be independent of diagnostic status, i.e. uniform across psychiatric and healthy populations (Grant et al., 2011; van Harmelen et al., 2014; van Harmelen et al., 2013), suggesting that maltreatment effects may be instantiated early in life, persist into adulthood, and augment the expression of neural abnormalities within the PTSD diagnosis.

To address these questions, we re-conceptualized a well-characterized emotional conflict paradigm (Etkin et al., 2006) as a probe of emotional valence processing in interaction with goal relevance (Fig. 1) to parse heterogeneity in PTSD as a function of maltreatment history. Hereafter in this manuscript, the term “valence” refers to the difference between fear and happy stimuli (e.g., word valence refers to the difference between the fear and happy words). More specifically, beyond examining CM effects on conflict detection and adaptation, we were interested in how neural valence processing varied as a function of whether valence was perceived as a distractor (emotion word) or as the target of attention (emotional facial expression). By investigating the paradigm as a function of face and word valence in addition to congruence, we are able to address questions regarding how maltreatment history impacts emotional valence neural processing within PTSD as a function of attentional focus towards emotional stimuli in the service of a behavioral goal, i.e. task relevance. Such an approach may prove useful in addressing existing questions regarding the interaction of goal-relevance with valence processing in PTSD and the neural basis of variability in attention biases to threat.

We tested conflict and valence-processing effects in a group of trauma-exposed healthy controls (TEHCs) as well as a large sample of PTSD patients, of which we separated those self-reporting a moderate-to-severe history of childhood maltreatment (PTSD-CM). This approach enables inference both on the impact of maltreatment history on neural function within the PTSD diagnosis (PTSD-CM vs. PTSD) as well as the effects of diagnosis only on valence processing (PTSD vs. TEHCs). Given compelling cross-species evidence for early life stress promoting increased amygdala reactivity to threat that interferes with goal-oriented behavior (Malter Cohen et al., 2013), we predicted that PTSD-CM relative to PTSD patients would display increased amygdala activation to negative valence in the context of implicit valence processing (emotional word) irrespective of target valence, i.e. a main effect of word valence. Additionally, consistent with the role of the dlPFC in augmenting attention processes in the context of valence-related amygdala reactivity (Comte et al., 2016) and prior findings for maltreatment effects on dlPFC function (Gatt et al., 2010; Marusak et al., 2015), we expected the PTSD-CM group relative to the PTSD group to display altered dlPFC valence-related activation in interaction with goal-relevance (interaction of valence and face/word presentation). Our overall aim is to shed light on substantial diagnostic heterogeneity in amygdala-prefrontal responses as a function of this potent disorder risk factor.

2. Methods

2.1. Participants

The Stanford University Institutional Review Board approved the present study, which was carried out in accordance with the latest version of the Declaration of Helsinki. Sixty-six participants (20 Trauma Exposed Healthy Controls (TEHC) and 42 medication-free PTSD patients, 22 of which we grouped into a high childhood maltreatment group (PTSD-CM), as described below) were recruited through print and online advertisement (Table 1). Experienced PhD-level clinicians established DSM-IV diagnoses using the Clinician-Administered PTSD Scale for PTSD (CAPS (Blake et al., 1995)) and the Structured Clinical Interview for DSM-IV Diagnosis for non-PTSD diagnoses (SCID-IV (First et al., 2012)). IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI; (Wechsler, 1999)). Participants with PTSD were permitted to meet diagnostic criteria for comorbid mood and anxiety disorders secondary to PTSD, and history of substance dependence was permitted, given that abstinence had been maintained for more than three months. TEHCs were those participants who had experienced a lifetime traumatic event and did not develop significant symptoms of psychopathology (such as PTSD or acute stress disorder) as a consequence of the event. Furthermore, these subjects did not meet lifetime criteria for any other mental disorder. None of the patients had taken regular psychotropic medications at the time of scanning (free for at least 60 days prior), and those patients that took benzodiazepines had not taken any within 48 h of study appointments.

2.2. General inclusion and exclusion criteria

Inclusion criteria for all participants encompassed the following: eligibility for scanning (i.e., no metal embedded in body, not currently pregnant, no history of severe claustrophobia), no thyroid or opioid medication, good English comprehension, experience of a lifetime DSM-IV Criterion A traumatic event, and intellectual function adequate for comprehension of experimenter instructions. Exclusion criteria for all participants involved: lifetime diagnosis of psychosis, bipolar disorder, intellectual disability, neurodevelopmental disorders, history of neurological conditions or organic mental disorder (e.g., stroke, seizures, tumor, intracranial hemorrhage, multiple sclerosis), and current substance dependence.

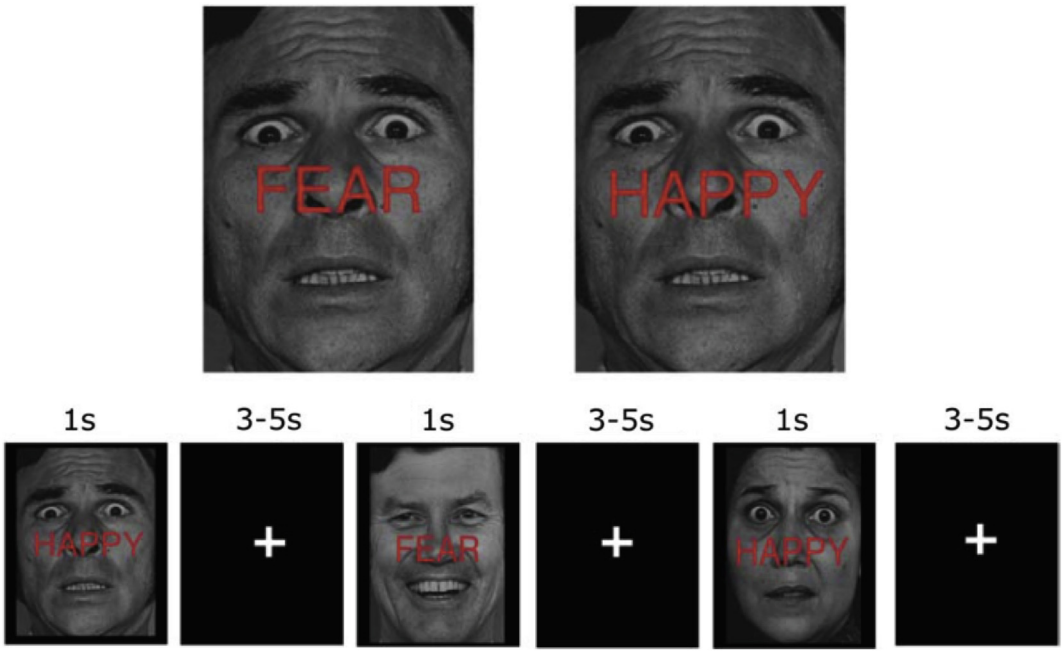

Fig. 1. Emotional Conflict Task. Participants were instructed to identify the underlying facial emotion (fearful or happy) while ignoring an overlying emotion distractor (emotion word - "fear" or "happy"). Trials varied such that emotional distractor words either matched or conflicted with the underlying facial expression.

Table 1
Sample demographics and task behavioral data by diagnostic group.

	PTSD-CM (n = 22)		PTSD (n = 20)		TEHC (n = 20)		Statistics	
	Mean	SD	Mean	SD	Mean	SD	F/x^2	p
Age (yrs)	39.71	10.80	37.09	10.37	32.48	12.45	2.21	0.12
Yrs of Educ	16.32	2.80	15.10	2.38	15.20	2.24	1.56	0.22
Gender	17 F		11 F		8 F		2.28	0.13
	5 M		9 M		12 M			
Full Scale IQ (WASI)	113	12.84	110	10.03	115	10.91	0.78	0.46
CAPS Total	72.27	15.11	61.95	13.61	2.30	3.60	201.48	0.00
CAPS ReExp	18.27	6.17	16.60	6.15	0.70	1.34	73.07	0.00
CAPS EffAvd	10.55	3.14	7.80	3.67	0.00	0.00	78.76	0.00
CAPS Numb	20.09	7.06	16.60	5.82	0.55	1.40	76.22	0.00
CAPS Hyper	23.36	4.54	20.95	5.80	1.05	2.16	155.75	0.00
Overall Task Accuracy	0.95	0.05	0.95	0.04	0.96	0.05	0.19	0.83
Hf Reaction Time (sec)	0.95	0.32	0.82	0.13	0.86	0.16	1.97	0.15
Fh Reaction Time (sec)	0.95	0.29	0.84	0.13	0.85	0.15	1.86	0.17
Ff Reaction Time (sec)	0.87	0.28	0.76	0.12	0.79	0.14	1.81	0.17
Hh Reaction Time (sec)	0.87	0.26	0.76	0.11	0.78	0.14	1.88	0.16
iI Reaction Time (sec)	0.93	0.29	0.82	0.13	0.85	0.15	1.69	0.19
cI Reaction Time (sec)	0.95	0.29	0.83	0.13	0.86	0.15	2.16	0.12
CTQ Emotional Abuse	19.82	4.39	10.70	5.07	9.55	4.86	29.60	0.00
CTQ Emotional Neglect	19.64	3.46	11.35	4.02	9.75	3.29	46.27	0.00
CTQ Physical Abuse	14.91	5.33	7.75	3.77	8.40	4.53	15.67	0.00
CTQ Physical Neglect	13.14	4.04	7.45	2.26	6.75	1.83	30.60	0.00
CTQ Sexual Abuse	15.64	6.51	6.65	4.07	7.65	6.11	15.91	0.00
CTQ Total	83.14	15.34	43.90	11.52	42.10	14.35	59.41	0.00

Educ = education; Yrs = years; F = female; M = male; CAPS=Clinician Administered PTSD Scale for DSM-IV; EffAvd = effortful avoidance; Hyper = hyperarousal; Numb = numbing; ReExp = re-experiencing; PTSD-CM = posttraumatic stress disorder with high childhood maltreatment; PTSD = posttraumatic stress disorder without high childhood maltreatment; TEHC = trauma-exposed healthy control; Hf = happy face, fear word; Fh = fear face, happy word; Hh = happy face, happy word; Ff = fear face, fear word; iI = post-incongruent incongruent trials; cI = post-congruent incongruent trials; WASI=Wechsler Abbreviated Scale of Intelligence.

2.3. Self-report questionnaire

Childhood Trauma Questionnaire (CTQ). The CTQ (Bernstein et al., 1997) is a 28-item, brief, reliable and valid self-report instrument assessing sexual, physical and emotional abuse and physical and emotional neglect in childhood. Scores are calculated for none, mild, moderate, and severe for each type of abuse and neglect. We categorized those PTSD patients into the PTSD-CM group when they met criteria for moderate to severe childhood maltreatment in 3 or more of the 5 assessed domains (sexual, physical and emotional abuse and physical and emotional neglect). The moderate to severe cutoff is an effective method for distinguishing significant maltreatment exposure in individuals (Bernstein et al., 1997).

We utilized a group difference approach to test neural processing as a function of PTSD diagnosis as well as maltreatment

history within the PTSD diagnosis. Splitting the PTSD sample based upon moderate to severe maltreatment in three or more domains allowed for good discriminability in this sample between PTSD diagnosis and maltreatment history within PTSD. Specifically, CTQ total scores were nearly equivalent between the PTSD and TEHC groups, while the PTSD-CM group displayed significantly higher scores relative to both other groups (see Table 1 and Results section for further details).

2.4. Neuroimaging paradigm

Emotional Conflict Task (Fig. 1). We re-conceptualized a well-characterized emotion conflict task (Etkin et al., 2006) to also assess valence processing as a function of goal relevance (emotional facial expression is a goal-relevant target, emotional word is a goal-irrelevant distractor) in addition to standard conflict and conflict adaptation effects (Etkin et al., 2006). Participants were instructed to identify the underlying facial emotion (fearful or happy) while ignoring an overlying emotion distractor (emotion word - "FEAR" or "HAPPY"). Trials varied such that emotional distractor words were either congruent or incongruent with the underlying facial expression. Each task consisted of 148 presentations of facial photographs drawn from a set by Ekman (Ekman, 1976). Stimuli were presented for 1000 milliseconds (ms) with a varying inter-stimulus interval of 3000–5000 ms in a pseudo-randomized order counterbalanced for facial expression, gender, word, and response button. All participants of the study went through the tasks outside the scanner to ensure proficiency (minimum 80% accuracy) was reached and the task instructions were understood.

2.5. MRI data acquisition

Images were acquired on a 3-T GE Signa scanner using a custom-built head coil. During task completion, twenty-nine slices (4.0 mm thickness, 0.5 mm gap) were acquired in the axial direction across the whole brain using a T2*-weighted gradient echo spiral pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 80°, 1 interleaf, field of view = 22 cm, 64 × 64 matrix). A high-resolution T1-weighted image (three-dimensional inversion recovery spoiled gradient-recalled acquisition in the coronal place with the following parameters: inversion time = 300 ms, TR = 8 ms, TE = 3.6 ms, flip angle = 15°, field of view = 22 cm, 124 slices, matrix = 256 × 192, number of excitations = 2, acquired resolution = 1.5 × 0.9 × 1.1 mm) was likewise obtained for each participant. During the emotion conflict task, measures of heart rate and respiration were collected and used to remove physiological noise from the voxelwise time series (Glover et al., 2000).

2.6. Preprocessing and individual-level analysis

Data were preprocessed using FSL tools (Jenkinson et al., 2012). Affine transformation of functional to structural images using boundary-based registration based upon tissue segmentation as implemented in FSL's FLIRT was added to non-linear normalization of each participant's T1 image to MNI152 using FNIRT from FSL 5.0 (Andersson et al., 2007). Functional images were subsequently aligned to the middle volume of the run. Global signal corresponding to segmented white matter and CSF was regressed out of motion-corrected functional images, which were isotropically smoothed with a 6 mm full-width half max (FWHM) Gaussian kernel to account for individual anatomical variability.

Separate regressors convolved with the hemodynamic response function (HRF) were modeled corresponding to trials as a function of face and word valence, i.e. fear word with fear face, fear word with happy face, etc. We hereafter refer to the valence of the distractor word on each trial using a lower-case letter (f = fear; h = happy) and the valence of the target face as a capital letter (F = fear; H = happy). For example, a fear face with a fear word is referred to as Ff, while a fear face with a happy word is referred to as Fh, etc. We examined the effects of emotional valence on neural reactivity through conducting a first-level GLM analysis using SPM 8.0 that specified trial types as a function of face, word valence, and previous trial congruence (incongruent or congruent), combined with six motion regressor parameters of no interest. This resulted in eight trial types (post-congruent Ff, post-incongruent Ff, post-congruent Fh, post-incongruent Fh, post-congruent Hh, post-incongruent Hh, post-congruent Hf, post-incongruent Hf). Our a-priori within-subject contrasts of interest were: a) incongruent vs. congruent (conflict); b) post-incongruent incongruent vs. post-congruent incongruent (conflict adaptation); c) valence of emotional distractor averaged over target valence, i.e. fear word (Ff + Hf) vs. happy word (Fh + Hh); d) valence of the emotional face averaged over distractor valence, i.e. fear face (Ff + Fh) vs. happy face (Hh + Hf); and e) valence effects (fear vs. happy) in interaction with goal-relevance (face vs. word), i.e. the difference in valence processing as a function of stimulus presentation.

2.7. Group-level analyses

2.7.1. Group comparisons

Voxelwise group-level analyses were conducted in *a-priori* anatomical ROIs informed by the functional neuroanatomy of PTSD (Patel et al., 2012). For each within-subject contrast presented above, second-level analyses were applied to test the omnibus F statistic corresponding to the effect of group. Statistical significance was established using threshold-free cluster enhancement (TFCE) with permutation testing implemented in FSL (Smith and Nichols, 2009). TFCE yields a voxelwise estimate of the cluster-like local spatial support and eliminates the need for setting an arbitrary voxelwise clustering threshold, thought to provide a more sensitive measure of activation (Smith and Nichols, 2009). The output image represents a TFCE "value" at every voxel. Consequently, the thresholded TFCE output image improves discrimination between noise and spatially extended signal. We first computed TFCE images for the task effects of conflict, conflict adaptation, face valence, word valence, and the face x word valence interaction using permutation testing with a sign-flip (analogous to a one-sample t-test). In order to yield critical values for statistical inference, we conducted separate permutation tests with 5000 random permutations for the omnibus effect of group across *a priori* stereotactically-defined anatomical ROIs bounded using meta-analytic findings (Patel et al., 2012). These encompassed the bilateral amygdala, bilateral anterior insula (anterior to y = 0), ventromedial prefrontal cortex (anterior cingulate inferior to z = 10), dorsal anterior cingulate (anterior and mid-cingulate cortex superior to z = 28 and within −8 < y < 24), and bilateral dlPFC (left and right inferior and middle frontal gyri at z > 18, x > +/− 30, and y < 24). Subsequently, we corrected voxelwise significance values for multiple comparisons, with the ultimate criterion being a two-sided family-wise error (FWE) corrected $p < 0.05$ for the omnibus F statistic corresponding to the effect of group. Additional whole-brain exploratory analyses were also conducted within gray matter using the same significance criterion. Average contrast coefficients were extracted from TFCE-enhanced "clusters" of significant difference for the omnibus effect of group within each subject.

2.7.2. Brain-symptom severity relationships

In order to assess potential clinical significance of neural activation differences within the PTSD sample, associations between

symptom measures were assessed in relation to brain activation that differed as a function of maltreatment history. Specifically, for regions displaying a significant effect of group that corresponded to differences between PTSD-CM and PTSD participants, we used cluster beta weights extracted from each participant as a within-subject measure of activation and correlated these weights with PTSD symptom dimensions derived from CAPS (corresponding to the four-factor model of re-experiencing, effortful avoidance, numbing, and hyperarousal (King et al., 1998)) within the PTSD-CM and PTSD groups separately using IBM SPSS version 21.0. For relationships that displayed significant non-parametric correlations with one PTSD group but not the other, we conducted a subsequent moderation analysis using linear regression across both groups with the following factors: CAPS subscale (mean-centered), diagnostic group (effects-coded), and the interaction of CAPS subscale with diagnostic group.

2.8. Psychophysiological interaction (PPIs)

In order to provide a network perspective on regional activation differences, we conducted PPI analyses to examine context-dependent task connectivity with seed regions that displayed differential activation between PTSD-CM and PTSD participants. A mask of regional activation differences derived from the omnibus group effect activation analysis was used to extract a subject-specific time series from each participant. This time course was then deconvolved and the interaction of the seed region time series with the effects-coded contrast of interest (the contrast within which activation differences for the seed region(s) were observed) was then calculated (a psychophysiological interaction). This PPI was then convolved with the hemodynamic response function and entered into another first-level analysis in SPM 8.0 along with regressors corresponding to the seed region time series, the contrast of interest, and six motion nuisance regressors. The outcome measure of interest was the beta coefficient corresponding to the PPI. These within-subject maps of PPI beta coefficients were then carried to a second-level TFCE analysis (as described above), with the criterion of significance being the FWE-corrected $p < 0.05$ for the omnibus F statistic corresponding to the effect of group.

3. Results

3.1. Demographics, symptom measures, and task behavior

The PTSD-CM, PTSD, and TEHC groups were well matched on age, gender, and education level (Table 1). We categorized those PTSD patients into the PTSD-CM group when they met criteria for moderate to severe childhood maltreatment in 3 or more of the 5 domains of the Childhood Trauma Questionnaire. This resulted in the PTSD-CM group having significantly higher levels of maltreatment across all 5 CTQ domains as well as the total score (multivariate ANOVA Games Howell corrected post-hoc comparisons: all $p's < 0.001$), while the PTSD and TEHC participants did not differ on any maltreatment domain (all $p's > 0.344$). Both PTSD groups also displayed greater PTSD symptoms as assessed by CAPS on all symptom domains (Games Howell corrected post-hoc comparisons: all $p's < 0.001$). Relative to the PTSD group, the PTSD-CM group displayed equivalent frequency of comorbid major depressive disorder (two-tailed Fisher's exact test $p = 1.00$) and similar levels of PTSD symptoms with the exception of the symptom domain of effortful avoidance (Games Howell corrected post-hoc comparison: $p = 0.04$), for which the PTSD-CM group displayed significantly higher levels. All other symptom PTSD symptom domains, as well as the total score, did not differ between the PTSD-CM and PTSD groups. Groups did not differ on performance of the behavioral paradigm (all $p's$ for omnibus effect of group > 0.14), demonstrating similar patterns of reaction time and accuracy for face/word conditions and for within-subject contrasts of face/word conditions corresponding to imaging contrasts (e.g., incongruent vs. congruent, post-incongruent incongruent vs. post-congruent incongruent, fear vs. happy word, fear vs. happy face, face valence vs. word valence). Finally, the groups did not differ on IQ ($p = 0.462$).

3.2. Conflict detection and conflict adaptation task effects

3.2.1. Conflict detection

In the ROI analysis, the contrast of incongruent vs. congruent trials activated the bilateral anterior insula and dorsolateral prefrontal cortex. The exploratory whole-brain analysis revealed additional activation in the bilateral cerebellum, left fusiform gyrus, bilateral temporoparietal junction, middle cingulate cortex, and precuneus. There were no regions more active for congruent vs. incongruent. See Table 2 for further details.

3.2.2. Conflict adaptation

In the ROI analysis, the contrast of post-incongruent incongruent trials vs. post-congruent incongruent trials revealed significant deactivation of the bilateral anterior insula, dorsal anterior cingulate, and bilateral dorsolateral prefrontal cortex. The exploratory whole-brain analysis revealed additional deactivation in the brainstem, left fusiform gyrus, right parahippocampal gyrus/amygdala, bilateral thalamus, bilateral putamen, cuneus, bilateral parietal lobule, middle cingulate cortex, and precuneus. There were no regions more active for post-incongruent incongruent vs. post-congruent incongruent. See Table 2 for further details.

3.3. Group differences for conflict and conflict adaptation

There were no significant differences amongst the three groups observed in the ROI analyses or the exploratory whole-brain analysis for conflict detection or conflict adaptation.

3.4. Valence task effects

To better understand valence processing as a function of goal-relevancy, we first examined task effects for the main effect of face valence, the main effect of word valence, and the interaction of face and word valence across all participants (Table 2).

3.4.1. Word valence

For the effect of word valence (Fear > Happy) in *a-priori* ROIs and across the whole brain, we did not observe any significant activation. However, for the opposite contrast (Happy > Fear), in the whole-brain exploratory analysis we observed significant task-related engagement of the bilateral visual cortex. No regions of activation were observed in the ROI analysis.

3.4.2. Face valence

For the effect of face valence (Fear > Happy) in *a-priori* ROIs, we observed significant activation in the left anterior insula. We did not observe any significant effects on the whole-brain analysis. For the opposite effect (Happy > Fear) in *a-priori* ROIs and across the whole brain, we did not observe any significant activation.

3.4.3. Interaction of face and word valence

Finally, we tested for differences in valence processing as a function of goal-relevancy (face vs. word). We did not observe any regions that were more responsive to face or word valence across the entire sample in *a-priori* ROIs, but in the whole brain analysis

Table 2
Task Activation by contrast.

Direction	Mask	Hem.	MNI atlas region(s)	Voxels in cluster	X	Y	Z	Voxelwise stats			
								T		*p*	
								Mean	*SD*	*Mean*	*SD*
Incongruent (Inc) vs. Congruent (Con)											
Inc > Con	ROI	L	Inferior/Middle Frontal Gyri	1145	−46	9	32	4.03	0.86	0.003	0.005
Inc > Con	ROI	L	Insula Lobe	925	−37	13	5	4.64	0.99	0.002	0.004
Inc > Con	ROI	R	Insula Lobe	760	39	15	5	4.68	0.93	0.002	0.004
Inc > Con	ROI	R	Inferior/Middle Frontal Gyri	225	44	9	30	3.60	0.31	0.014	0.005
Inc > Con	WB	L	Inferior/Middle Frontal Gyri/Insula Lobe	4611	−40	10	23	3.94	0.93	0.007	0.008
Inc > Con	WB	L	Middle Occpital Gyrus/Superior Occipital Gyrus/Middle Temporal Gyrus/Superior Temporal Gyrus/Supramarginal Gyrus/Angular Gyrus/Inferior Parietal Lobule	4552	−40	−54	29	3.53	0.58	0.010	0.007
Inc > Con	WB	R	Insula Lobe/Inferior Frontal Gyrus	1210	39	17	7	4.66	0.77	0.009	0.008
Inc > Con	WB	R	Middle Temporal Gyrus/Superior Temporal Gyrus/Supramaringal Gyrus	620	54	−42	22	3.61	0.34	0.020	0.003
Inc > Con	WB	R	Inferior Parietal Lobule	127	34	−45	43	3.56	0.16	0.024	0.008
Inc > Con	WB	L/R	Middle Cingulate Cortex	113	0	−23	27	4.99	0.19	0.021	0.002
Post-Incongruent Incongruent (iI) vs. Post-Congruent Incongruent (cI)											
cI > iI	ROI	R	Inferior/Middle Frontal Gyri	1040	45	11	34	4.09	0.79	0.002	0.004
cI > iI	ROI	L/R	Middle Cingulate Cortex	403	−1	11	40	3.69	0.48	0.008	0.007
cI > iI	ROI	L	Inferior/Middle Frontal Gyri	246	−44	6	34	3.49	0.32	0.015	0.006
cI > iI	ROI	R	Insula Lobe	172	33	21	2	4.16	0.51	0.007	0.006
cI > iI	ROI	L	Insula Lobe	76	−32	21	2	4.22	0.31	0.012	0.006
cI > iI	WB	L/R	Brainstem/Amygdala/Putamen/Insula Lobe/Thalamus/Caudate Nucleus/Inferior Frontal Gyrus/Middle Frontal Gyrus	8449	20	5	12	3.34	0.68	0.009	0.007
cI > iI	WB	L/R	Inferior Frontal Gyrus/Anterior Cingulate Cortex/Middle Cingulate Cortex/SMA/Precentral Gyrus/Postcentral Gyrus/Inferior Parietal Lobule/Superior Parietal Lobule	6212	−20	−5	48	3.42	0.67	0.010	0.008
cI > iI	WB	R	Angular Gyrus/Superior Parietal Lobule/Inferior Parietal Lobule	1586	27	−59	51	3.40	0.42	0.016	0.006
cI > iI	WB	L/R	Lingual Gyrus/Calcarine Gyrus	1472	2	−79	6	3.18	0.30	0.019	0.003
cI > iI	WB	L	Fusiform Gyrus	621	−37	−69	−15	3.37	0.36	0.019	0.004
cI > iI	WB	R	Middle Frontal Gyrus	200	32	54	5	3.16	0.34	0.023	0.002
cI > iI	WB	L	Cerebellum	97	−14	−78	−37	3.17	0.12	0.024	0.001
cI > iI	WB	L	Middle Occipital Gyrus	40	−32	−94	10	3.31	0.15	0.025	0.001
Fear vs. Happy Word											
H > F	WB	R	Lingual Gyrus/Calcarine Gyrus	574	13	−84	−2	4.17	0.52	0.014	0.006
H > F	WB	L	Lingual Gyrus/Calcarine Gyrus	361	−13	−81	−6	4.12	0.54	0.017	0.006
Fear vs. Happy Face											
F > H	ROI	L	Insula Lobe	25	−33	10	14	4.15	0.53	0.016	0.005
Face Valence vs. Word Valence											
Fa > Wd	WB	L/R	Lingual Gyri/Calcarine Gyri/Fusiform Gyri	1194	4	−81	−5	3.91	0.34	0.017	0.004

X, Y, and Z are the MNI coordinates for the cluster center of mass; Voxelwise stats report mean cluster T and p voxelwise values with standard deviations; Direction indicates the directionality of positive effects; F = fear; Fa = Face; H = happy; Hem = hemisphere; L = left; R = right; ROI = region of interest masks; sd = standard deviation; WB = whole-brain mask; Wd = Word.

the bilateral visual cortex displayed greater activation to face valence relative to word valence. There were no regions in the ROI analysis or exploratory whole brain analysis that displayed greater activation to word valence vs. face valence.

3.5. Group differences for valence processing

3.5.1. Word valence

Inconsistent with our hypothesis for an amygdala activation difference in processing of goal-irrelevant stimulus valence as a function of maltreatment history, there were no significant differences observed for the processing of word valence in *a-priori* ROIs or across the whole brain. To explore whether this null finding might reflect insufficient power, we followed up the voxelwise exploration of the omnibus effect of group by testing a voxelwise contrast comparing the PTSD-CM and PTSD groups in *a priori* ROIs. This analysis did reveal a significant FWE-corrected pairwise difference between the PTSD-CM and PTSD groups in the left basolateral portion of the amygdala (15 voxels, $x = -19$, $y = -3$, $z = -27$), wherein the PTSD-CM group displayed greater activation to the fear word as compared to the happy word, whereas the PTSD group displayed the opposite pattern. However, the omnibus group effect in this region was not significant.

3.5.2. Face valence

There were no significant effects of maltreatment history on the processing of face valence in *a-priori* ROIs or across the whole brain.

3.5.3. Interaction of face and word valence

Next, we examined the interaction of face and word valence (fear vs. happy) for maltreatment-related differences to test the hypothesis that maltreatment history would augment dlPFC activation to emotional valence as a function of goal relevance. Consistent with our hypothesis, we observed a face x word valence interaction effect in the left dlPFC (Table 3; Fig. 2). Post-hoc extractions revealed this effect was due to greater activation in the left dlPFC to the face valence effect (greater activation to fear vs. happy) in the PTSD participants with the opposite pattern for word valence (greater activation to happy vs. fear). In contrast, PTSD-CM participants displayed greater activation to word valence (fear vs. happy) with more equivalent activation to face valence (fear vs. happy, with slightly greater activation to fear). TEHC participants displayed nearly equivalent activation to both face and word valence. Comparison of post-hoc extracted beta weights for face vs. word valence and each valence effect separately (face and word) revealed that the PTSD group significantly differed from both the PTSD-CM and TEHC participants for the face vs. word valence contrast (Games-Howell corrected post-hoc comparisons for PTSD vs. PTSD-CM: $p = 0.001$; and for PTSD vs. TEHC: $p = 0.045$). For the difference between PTSD

Table 3
Maltreatment-Related PTSD Activation Abnormalities (PTSD-CM vs. PTSD).

Mask	Hem.	MNI atlas region	Voxels in cluster	X	Y	Z	Voxelwise stats			
							F		*p*	
							Mean	*SD*	*Mean*	*SD*
Incongruent (Inc) vs. Congruent (Con)										
_	–	No sig. effects	–	–	–	–	–	–	–	–
Post-Incongruent Incongruent (iI) vs. Post-Congruent Incongruent (cI)										
_	–	No sig. effects	–	–	–	–	–	–	–	–
Fear vs. Happy Word										
_	–	No sig. effects	–	–	–	–	–	–	–	–
Fear vs. Happy Face										
_	–	No significant differences	–	–	–	–	–	–	–	–
Face Valence vs. Word Valence										
ROI	L	Inferior frontal gyrus	8	−43	4	27	8.33	0.28	0.047	0.001

X, Y, and Z are the MNI coordinates for the cluster center of mass; Voxelwise stats report mean cluster T and p voxelwise values with standard deviations; Hem = hemisphere; L = left; PTSD = posttraumatic stress disorder; PTSD-CM = posttraumatic stress disorder with high exposure to childhood maltreatment; R = right; ROI = region of interest masks; sd = standard deviation; WB = whole-brain mask.

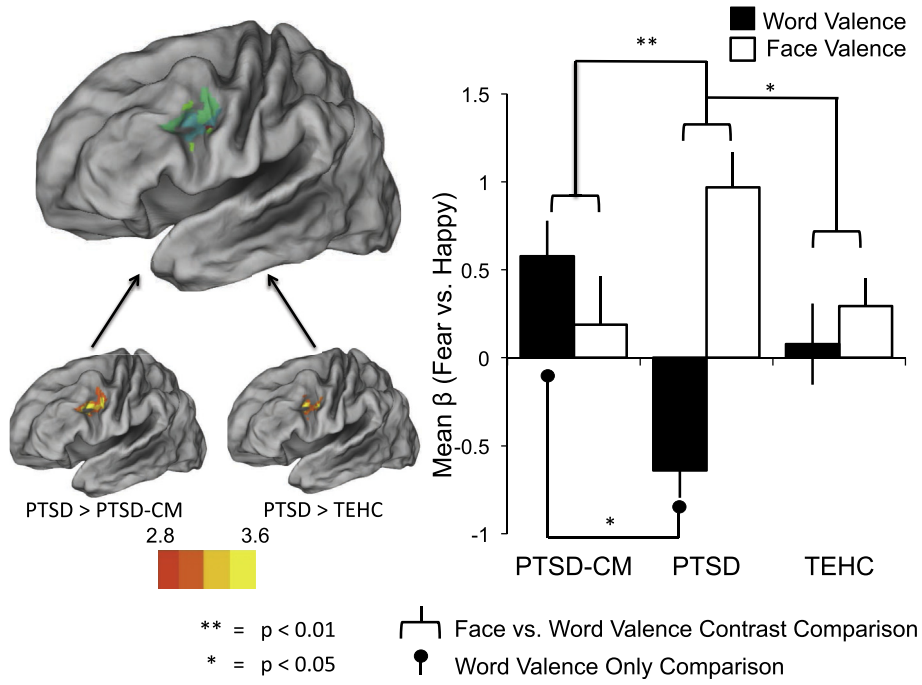

Fig. 2. Maltreatment Effects on Left Dorsolateral Prefrontal Activation to Face vs. Word Valence in PTSD. Figure depicts differences in left dorsolateral prefrontal activation differences as a function of valence differences for Face vs. Word stimuli. Area in red is the omnibus effect of group, area in seafoam green is comparison for PTSD > PTSD-CM, area in yellow-green is the comparison for PTSD > TEHC, and area in blue-green is the conjunction of the two pairwise comparisons, show below. Error bars represent ± 1 standard error. Lines and asterisks above bars on bar graph indicate significant differences amongst pairwise comparisons of face vs. word valence activation differences and word valence activation by group. Color bar represents t-values for the voxel wise pairwise comparisons displayed. PTSD = posttraumatic stress disorder; PTSD-CM = posttraumatic stress disorder with high exposure to childhood maltreatment; TEHC = trauma-exposed healthy controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and PTSD-CM participants, this effect arose from dlPFC response to word valence (Omnibus $F(2,59) = 3.210$, $p = 0.048$; Games-Howell corrected post-hoc comparison for PTSD vs. PTSD-CM: $p = 0.021$) but not face valence (Omnibus $F(2,59) = 1.251$, $p = 0.294$; Games-Howell corrected post-hoc comparison for PTSD vs. PTSD-CM: $p = 0.37$). Furthermore, TEHCs did not differ from the PTSD-CM group for the face vs. word valence effect (Games-Howell corrected post-hoc comparison: $p = 0.66$), and TEHCs did not differ from either group when valence effects were examined separately for word and face (all $p's > 0.29$). Finally, the omnibus group effect for word valence was not significant for either word alone (all $p's > 0.79$), indicating this effect arose from the difference between the two conditions (see Supplemental Fig. 1).

3.6. Relationship of maltreatment-related abnormalities to PTSD symptoms

To explore the clinical significance of maltreatment-related abnormalities, we individually correlated PTSD symptom dimensions with post-hoc extracted individual beta-weights from clusters displaying significant activation differences between the PTSD-CM and PTSD groups, using the four factor CAPS symptom parcellation model of re-experiencing, effortful avoidance, numbing, and hyperarousal (King et al., 1998). We observed that left

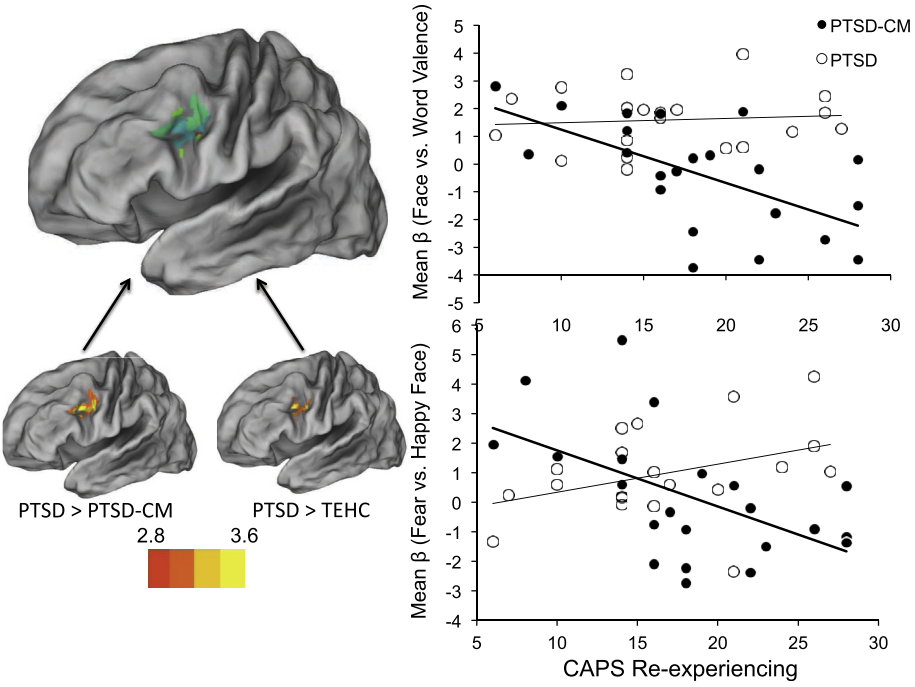

Fig. 3. Maltreatment Status Moderates Relationship Between Left Dorsolateral Prefrontal Activation to Goal-Relevant Stimulus Valence and Re-experiencing Symptoms. Figure depicts an interaction between maltreatment status (PTSD-CM vs. PTSD) and relationship between omnibus *F* statistic-defined left dorsolateral prefrontal activation differences to: a) face vs. word valence; and b) fear face vs. happy face, both with CAPS re-experiencing symptoms. CAPS=Clinician-Administered PTSD Scale; PTSD = posttraumatic stress disorder; PTSD-CM = posttraumatic stress disorder with high exposure to childhood maltreatment; TEHC = trauma-exposed healthy controls.

dlPFC activation to the difference between face (Fear Face vs. Happy Face) and word valence (Fear Word vs. Happy Word) effects (face x word valence interaction) was negatively associated with CAPS re-experiencing symptoms in the PTSD-CM group (Spearman's rho = −0.65, $p = 0.001$; Fig. 3). That is, greater symptoms of re-experiencing were associated with less left dlPFC activation to face valence relative to word valence. Further exploring this effect by splitting face and word valence into separate conditions, we observed this relationship arose from a significant negative correlation between face valence and re-experiencing symptoms (Spearman's rho = −0.60, $p = 0.003$), but no relationship with word valence (Spearman's rho = 0.24, $p = 0.28$). We observed no significant correlation between left dlPFC activation and CAPS re-experiencing symptoms in the PTSD group for the difference between the face and word valence (Spearman's rho = 0.08, $p = 0.73$), nor for face valence (Spearman's rho = 0.37, $p = 0.11$) or word valence separately (Spearman's rho = 0.32, $p = 0.17$). Maltreatment status also moderated this relationship in a linear regression incorporating an interaction term, both for face vs. word valence ($t(38) = 2.941$, $p = 0.006$) and face valence alone ($t(38) = 3.282$, $p = 0.002$). This effect continued to remain significant when controlling for other PTSD symptom dimensions in the same model for both face vs. word valence ($t(35) = 3.10$, $p = 0.004$) and for face valence alone ($t(35) = 2.89$, $p = 0.007$).

3.7. Context-dependent left dorsolateral prefrontal connectivity

We used a mask of the omnibus group effect in the left dlPFC for face vs. word valence to interrogate group differences in context dependent prefrontal connectivity. Since activation differences arose primarily from the word valence contrast, we examined connectivity with the left dlPFC seed region for both the word valence contrast and the face vs. word valence contrast. However, neither contrast yielded significant differences in left dlPFC context-dependent connectivity amongst groups in the ROI analysis nor the whole brain analysis.

3.8. Exploring the effect of effortful avoidance symptom severity group differences on findings

As the PTSD-CM group displayed significantly higher levels of CAPS effortful avoidance symptoms, we attempted to see if group differences between the PTSD-CM and PTSD groups could be better attributed to differences in effortful avoidance symptoms or maltreatment history. To do so, we used a multiple regression with post-hoc extracted beta weights from the dlPFC group effect to examine whether CAPS effortful avoidance symptoms or CTQ total score better accounted for neural differences across the PTSD sample. In the left dlPFC, CTQ total score was a significant predictor of activation across the PTSD sample when controlling for CAPS effortful avoidance ($t(39) = -2.06$, $p = 0.046$), but CAPS effortful avoidance was not ($t(39) = -1.35$, $p = 0.19$). These analyses demonstrate group differences in neural reactivity are more strongly accounted for by maltreatment history as opposed to differences in PTSD symptom severity.

4. Discussion

Here, we assessed the effects of maltreatment history on conflict and emotional valence processing in a large sample of PTSD patients stratified by goal-relevancy, i.e. whether stimulus emotional valence was relevant (face) or irrelevant (word) to task demands. This study produced the following primary findings. First, maltreatment history was associated with left dlPFC activation to the interaction of valence and goal-relevancy within PTSD, such that: a) the PTSD group displayed greater activation to goal-relevant negative face valence and prominent deactivation to goal-irrelevant negative word valence (i.e., greater activation for

happy relative to fear word); while b) the PTSD-CM group displayed greater activation to goal-irrelevant negative word valence (fear vs. happy) and nearly equivalent activation to goal-relevant faces irrespective of valence. Second, maltreatment history moderated relationships between dlPFC activation differences and PTSD symptom dimensions such that less activation to goal-relevant stimulus valence was associated with greater PTSD symptoms of re-experiencing in PTSD-CM participants. In aggregate, these findings provide initial evidence that maltreatment history accounts for heterogeneity in PTSD neurocircuitry implicated in regulation of automatic attentional orienting, and variability in this circuit may influence expression of PTSD symptom dimensions.

We observed that left dlPFC activation was differentially responsive to the effect of valence from goal-relevant vs. goal-irrelevant emotional stimuli as a function of maltreatment history within the PTSD sample, with the PTSD-CM group displaying greater dlPFC engagement to negative valence when the stimulus was not the focus of task demands. This suggests dlPFC activation in this context may be compensatory and serve to augment or correct automatic attentional threat orienting. Activation in the dlPFC has been demonstrated to vary as a function of attentional demands in threat-related emotional contexts (Comte et al., 2016), supporting a role for this circuit in detection of environmental threat that is not the focus of conscious attention and subsequent disengagement of attention from the threat stimulus. If maltreatment does, in fact, promote greater difficulty in disengaging from threatening cues that interfere with goal-oriented behavior (as suggested in Malter Cohen et al., 2013), the increased dlPFC activation in the PTSD-CM relative to the PTSD group fits well with the interpretation that these individuals require greater cortical engagement to reorient attention to task relevant demands. Consistent with this interpretation, we observed that greater left dlPFC activation to the valence of goal-relevant stimuli in the PTSD-CM group was associated with fewer symptoms of re-experiencing, suggesting that greater deployment of cortical attention-orienting resources towards goal-relevant stimulus valence in these individuals may serve to buffer against re-experiencing symptoms, which by definition involve non-relevant, trauma-related information impinging on conscious experience. Taken together, these findings suggest that: a) severity of PTSD re-experiencing symptoms are influenced by valence-related attention modulating mechanisms instantiated in the dlPFC; and b) the maltreatment-induced shift of dlPFC attention modulation from goal-relevant stimulus valence to goal-irrelevant stimulus valence moderates this relationship between re-experiencing symptoms and dlPFC function.

Contrary to our hypothesis, we did not observe a significant omnibus group effect of goal-irrelevant stimulus valence on amygdala activation. Though an exploratory and less conservative voxel wise pairwise comparison analysis between PTSD-CM and PTSD participants did reveal an effect in the left amygdala, we hesitate to make any strong or interpretive statements regarding this finding. We speculate the current study may have been underpowered to detect such an effect, if such an effect is indeed present. Alternatively, the current paradigm (which incorporates valence processing in the context of conflicting stimuli) may not have been optimally suited to elicit such effects in the amygdala, which is thought to be less responsive to emotional stimuli in the context of task demands that require greater depth of conscious processing (Costafreda et al., 2008). Consistent with this interpretation, we did not observe any significant valence-related activation in the amygdala for either valence contrast, which suggests that the current paradigm may not have been optimally suited to engaging amygdala reactivity (perhaps due to the simultaneous presentation of multiple emotional stimuli, i.e. face and word). Instead, both conflict and valence contrasts maximally engaged sensory and prefrontal cortical regions while not strongly driving activity in subcortical limbic structures. However, the prominent cortical engagement induced by our emotional conflict paradigm (from both a conflict and valence-processing perspective) was apparently well suited to elicit differential dlPFC modulation of valence processing as a function of maltreatment history in PTSD, which is consistent with the prominent and persistent prefrontal alterations that are consequent to such forms of early life stress (De Bellis and Keshavan, 2003; Fonzo et al., 2013; Gatt et al., 2010; Miller et al., 2015; Taylor et al., 2006).

There are several limitations to the current study. First, although our groups were well matched on demographics, the PTSD-CM group displayed higher levels of effortful avoidance symptoms on CAPS, which could serve to confound group differences as a function of maltreatment. Post-hoc regression analyses suggest that symptom differences did not contribute to observed group differences in activation, but we are unable to definitively rule out this possibility. Second, the emotional conflict paradigm we utilized to assess valence processing in this sample does not allow for the disentanglement of valence effects due strictly to stimulus type (face vs. word) from those reflecting pure goal-relevancy (task relevant vs. task irrelevant). Future studies may wish to incorporate stimuli of congruent type as both the focus of task demands as well as irrelevant to task demands to disentangle these effects. Third, we used a group difference approach to test for the effects of CM. A continuous linear approach would have been an alternative (and potentially more powerful) method to characterize CM effects, but we favored the group difference approach as it better allows for the discrimination of neural effects related to maltreatment within PTSD from those that are better accounted for by diagnostic status. As the TEHC group displayed lower levels of maltreatment relative to the combined patient group and a more restricted range of CTQ scores, the assessment of continuous maltreatment relationships with brain function moderated by diagnostic status could confound effects of maltreatment with those of diagnosis and may also be conceptually problematic. Fourth, the absence of a trauma-unexposed healthy comparison group is a relative weakness, given that there is no appropriate comparison group to assess the influence of trauma exposure on task activation. Fifth, we did not exclude patients with comorbid mood/anxiety disorders from participation, which may limit specificity of findings to the PTSD diagnosis but is also more representative of the high comorbidity in traumatized populations.

In closing, these results highlight maltreatment history as an important source of heterogeneity in dorsolateral prefrontal brain function within PTSD in the context of emotional valence processing as a function of varying levels of attentional engagement. These findings contribute to a burgeoning literature demonstrating the importance of individual developmental characteristics in determining phenotypic expression of psychopathology (Teicher et al., 2013) and furthermore point towards implicit or automatic processing of threat as a construct malleable to maladaptive early life influences and as a candidate intervention target for a potential developmental PTSD phenotype.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2015.12.015.

Contributors

AE attained funding, conceived the study design and implementation and supervised all aspects of the present study and its analysis. GF recruited patients and supervised study procedures. GF and JH worked on data analyses. GF and JH wrote the manuscript, AE revised it. All authors have approved the final article.

Role of funding source

The funding source had no role in the planning, execution, analysis or manuscript preparation for this study.

Conflicts of interest

All of the authors declare no conflicts of interest.

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