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Amygdala response predicts trajectory of symptom reduction during Trauma-Focused Cognitive-Behavioral Therapy among adolescent girls with PTSD

Josh M. Cisler*, Benjamin A. Sigel, Teresa L. Kramer, Sonet Smitherman, Karin Vanderzee, Joy Pemberton, Clinton D. Kilts

Brain Imaging Research Center, Department of Psychiatry, University of Arkansas for Medical Sciences, USA

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ABSTRACT

Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT) is the gold standard treatment for pediatric PTSD. Nonetheless, clinical outcomes in TF-CBT are highly variable, indicating a need to identify reliable predictors that allow forecasting treatment response. Here, we test the hypothesis that functional neuroimaging correlates of emotion processing predict PTSD symptom reduction during Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT) among adolescent girls with PTSD. Thirty-four adolescent girls with PTSD related to physical or sexual assault were enrolled in TF-CBT, delivered in an approximately 12 session format, in an open trial. Prior to treatment, they were engaged in an implicit threat processing task during 3T fMRI, during which they viewed faces depicting fearful or neutral expressions. Among adolescent girls completing TF-CBT ($n = 23$), slopes of PTSD symptom trajectories during TF-CBT were significantly related to pre-treatment degree of bilateral amygdala activation while viewing fearful vs neutral images. Adolescents with less symptom reduction were characterized by greater amygdala activation to both threat and neutral images (i.e., less threat-safety discrimination), whereas adolescents with greater symptom reduction were characterized by amygdala activation only to threat images. These clinical outcome relationships with pre-treatment bilateral amygdala activation remained when controlling for possible confounding demographic or clinical variables (e.g., concurrent psychotropic medication, comorbid diagnoses). While limited by a lack of a control group, these preliminary results suggest that pre-treatment amygdala reactivity to fear stimuli, a component of neurocircuitry models of PTSD, positively predicts symptom reduction during TF-CBT among assaulted adolescent girls, providing support for an objective measure for forecasting treatment response in this vulnerable population.

Epidemiological studies suggest that ~50% of adolescents aged 12–17 have been exposed to physical assault, sexual assault, or witnessed violence, with ~6% of adolescent girls meeting criteria for posttraumatic stress disorder (PTSD) (Kilpatrick et al., 2000, 2003). Trauma-Focused Cognitive-Behavioral Therapy (TF-CBT) is the gold standard psychological treatment for trauma-exposed youth with symptoms of PTSD (Cohen et al., 2004, 2010, 2011). TF-CBT is typically delivered in 12–16 weekly sessions and is composed of modules including: psychoeducation about trauma and PTSD; parenting skills; affect regulation skills; and developing a narrative of the traumatic event and cognitive processing of associated thoughts and feelings. Numerous clinical trials have demonstrated efficacy for TF-CBT in reducing PTSD symptoms, depression, anxiety, and behavior problems (Cary and McMillen, 2012).

Despite clear efficacy, clinical response to TF-CBT is highly variable across individuals. These individual differences in clinical response are suggestive of variability in mediating psychopathology mechanisms among youth with PTSD. Identifying objective predictors that characterize variability in core mechanisms and that predict treatment response may help facilitate personalized treatment recommendations and may also help identify both the mechanisms of pediatric PTSD as well as the mechanisms most potently targeted in TF-CBT. Prior research demonstrates the viability of neuroimaging measures of brain function as biomarkers

* Corresponding author. Brain Imaging Research Center, Psychiatric Research Institute, University of Arkansas for Medical Sciences, 4301 W. Markham, #554, Little Rock, AR 72205, USA.
E-mail address: jcisler@uams.edu (J.M. Cisler).

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of adult PTSD treatment response. Bryant and colleagues found that greater pre-treatment amygdala reactivity to threat predicted less symptom reduction during CBT among a mixed-sex and mixed-trauma adult sample (Bryant et al., 2008a). A separate study among assaulted adult women with PTSD found a positive relationship between pre-treatment ACC activity during anticipation of negative images and treatment response to CBT (Aupperle et al., 2013). Finally, Falconer and colleagues found among a mixed-sex and mixed-trauma adult sample that greater activation of the striatum and ventrolateral PFC during an inhibitory control task predicted better treatment response to CBT (Falconer et al., 2013). Nonetheless, pre-treatment neural processing correlates of symptom reduction has not been investigated among adolescents with PTSD. Investigation of adolescents specifically is important given the substantial neurocognitive development that takes place in adolescence (Blakemore, 2012; Crone and Dahl, 2012; Paus et al., 2008) and knowledge of development-related difference in intrinsic brain organization (Dosenbach et al., 2010).

Neurocircuitry models of PTSD (Admon et al., 2013; Rauch et al., 2006) emphasize a hyperactive amygdala and dorsal anterior cingulate cortex (ACC) as brain mediators of hypervigilance for threat and heightened anxiety, and a hypoactive medial prefrontal cortex (mPFC) and hippocampus as brain mediators of deficits in emotion regulation and fear extinction. While TF-CBT was not developed to target these brain mechanisms explicitly, the behavioral phenomena targeted in TF-CBT (e.g., heightened anxiety, affect dysregulation, deficits in cognitive coping skills) map closely onto functional attributes of the neurocircuitry of PTSD. Given this overlap between the behavioral targets of TF-CBT and the neuroanatomy of PTSD, it could be expected that clinical response to TF-CBT would be related to pretreatment variability within this neurocircuit.

Here, we test the hypothesis that pre-treatment responsivity within the neurocircuitry mediating threat processing and implicated in PTSD (i.e., amygdala, dACC) predicts symptom reduction during TF-CBT among assaulted adolescent girls with a current diagnosis of PTSD. The prior imaging studies among adults (Aupperle et al., 2013; Bryant et al., 2008a; Falconer et al., 2013) suggest the hypothesis here among adolescents that lesser amygdala activity and greater ACC and striatum activity should predict greater symptom reduction during TFCBT. We chose fear stimuli as a commonly used probe of threat processing related to the heightened reactivity to threat stimuli associated with PTSD (Bryant et al., 2008b; Felmingham et al., 2010; Rauch et al., 2000). Focus on assault exposure was motivated by 1) the greater risk for psychopathology conferred via assault exposure relative to other types of traumas (Cisler et al., 2012), and 2) restriction to a specific type of trauma increases homogeneity of the sample. Focus on adolescent girls was motivated by 1) increased risk for PTSD following assault among girls relative to boys (Kilpatrick et al., 2003), 2) focus on a single sex increases homogeneity of the sample in light of known sex differences in brain function, and 3) adolescence is characterized by heightened stress reactivity and is a developmental period during which many forms of psychopathology, including mood and anxiety disorders, emerge (McCormick et al., 2010; McLaughlin et al., 2011; Ordaz and Luna, 2012).

1. Methods

1.1. Participants and assessments

Thirty-four adolescent girls, aged 11–16, meeting DSM-IV criteria for PTSD, having a positive history of assaultive violence exposure, and having a consistent caregiver with whom to participate in treatment, were enrolled in the study and began TF-CBT (see full enrollment flow chart in Supplemental Fig. 1). Participants were recruited through networking with local outpatient clinics, child advocacy centers, schools, juvenile justice, churches, and community organizations. Exclusion criteria consisted of MRI contraindications (e.g., internal ferrous metal objects), psychotic symptoms, lack of a consistent caregiver, and presence of a developmental disorder. Concurrent psychotropic medication was not exclusionary. Demographic and clinical characteristics of the sample are provided in Table 1. Adolescents provided assent and a caregiver/legal guardian provided consent. This study was conducted with IRB approval.

Participant's pre- and post-treatment mental health was assessed with the MINI-KID (Sheehan et al., 2010), a structured clinical interview for most Axis I disorders found in childhood and adolescence. Assaultive trauma histories were characterized using the trauma assessment section of the National Survey of Adolescents (NSA) (Kilpatrick et al., 2000; Kilpatrick et al., 2003), a structured interview used in prior epidemiological studies of assault and mental health functioning among adolescents that uses behaviorally specific dichotomous questions to assess sexual assault, physical assault, severe abuse from a caregiver, and witnessed violence. A trained female research coordinator with several years of experience with structured clinical interviews completed the MINI and NSA interviews with participants under the supervision of a licensed clinical psychologist.

The pre- and post-treatment assessment also included measures of verbal IQ (receptive one word picture vocabulary test (Brownell, 2000)), PTSD symptom severity (UCLA PTSD Reaction Index (Steinberg et al., 2004)), depression (Short Mood and Feelings Questionnaire (Angold et al., 1995); SMFQ), and emotion regulation ability using the Difficulty in Emotion Regulation Scale (Gratz and Roemer, 2004) (DERS). This measure of difficulty with emotion regulation consists of 5 subscales (Bardeen et al., 2012): clarity of emotions, difficulty engaging in goal-directed behavior while experiencing negative emotions, having limited strategies to regulate negative emotions, non-acceptance of negative emotions, and impulse control problems when experiencing negative emotions. Additionally, participants completed these same measures of PTSD and depression symptom severity prior to each therapy visit.

1.2. TF-CBT

TF-CBT was delivered by two postdoctoral clinical psychology fellows and a doctoral-level graduate student. The therapists were trained in TF-CBT according to an established protocol approved by Anthony Mannarino, Ph.D., a co-developer of TF-CBT, which included completion of TF-CBT*Web* (accessible at www.musc.edu/tfcbt) an online TF-CBT training, three days of in-person TF-CBT training with Dr. Mannarino, and one hour of weekly supervision with a licensed clinical psychologist with expertise in supervising the model. TF-CBT in this study used a 12-week protocol of 60–90 min weekly sessions.

MRI acquisition and Image Preprocessing. MRI acquisition and preprocessing steps are detailed in supplementary material.

1.3. fMRI tasks

Implicit Threat Processing Task. During this commonly used task (Williams et al., 2006), participants made button presses indicating gender decisions while viewing faces taken from the NimStim facial stimuli set [20]. The faces contained either neutral or fearful expressions, presented either overtly or covertly, in alternating blocks. There were an equal number of female and male faces. Overt faces were presented for 500 ms, with a 1200 ms inter-stimulus-

Table 1
Demographic, clinical characteristics, and treatment response of the samples.

	Treatment Completers (n = 23)		Completed ≥ 4 TF CBT sessions (n = 28)	
Variable	Mean/frequency (SD)		Mean/frequency (SD)	
Age	13.87 (1.77)		14.04 (1.67)	
Verbal IQ	95.26 (15.00)		95.04 (14.22)	
Ethnicity	39% Caucasian 52% African American 9% Biracial 0% Hispanic		39% Caucasian 50% African American 7% Biracial 4% Hispanic	
Total number of types of assaults	5.65 (3.98)		5.86 (4.34)	
Direct physical assault	96%		96%	
Sexual assault	87%		89%	
Witnessed violence	91%		93%	
Psychotropic medication	SSRI – 39% Antipsychotic – 17% SARI – 4% Alpha blocker – 4%		SSRI – 36% Antipsychotic – 18% SARI – 4% Alpha blocker – 4%	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Current PTSD	100%	35%	100%	–
# Comorbid diagnoses	2.74 (2.22)	1.00 (1.62)	2.93 (2.40)	–
Current anxiety disorder	65%	17%	64%	–
Current depressive disorder	52%	13%	50%	–
Current bipolar disorder	4%	0%	3%	–
Current alcohol use (past year)	8%	4%	14%	–
Current substance use (past year)	12%	17%	17%	–
Current conduct/ODD	26%	21%	32%	–
UCLA PTSD index	36.04 (17.87)	18.30 (16.62)	35.93 (17.74)	19.64 (16.25)
SMFQ	12.22 (8.25)	4.61 (6.55)	12.46 (8.06)	4.46 (6.00)
DERS Nonacceptance	9.61 (7.06)	3.48 (5.15)	10.43 (7.46)	–
DERS goals	11.65 (5.75)	4.57 (5.54)	12.46 (5.79)	–
DERS impulse	8.30 (6.89)	3.52 (5.39)	9.00 (6.67)	–
DERS strategies	12.57 (8.98)	5.09 (7.30)	13.18 (8.99)	–
DERS clarity	7.83 (5.35)	3.65 (4.99)	8.36 (5.46)	–

Note. SMFQ = Short mood and feelings questionnaire; DERS = Difficulties in Emotion Regulation Scale. Participants who dropped out prior to completing all TF-CBT modules (n = 5) did not receive a full post-treatment assessment and their post-treatment data are limited to the UCLA PTSD index and SMFQ.

interval displaying a blank screen with a fixation cross, in blocks of 8 presentations for a total block length of ~17 s. Covert face blocks used a similar design but were presented for 33 ms followed immediately by a neutral facial expression mask for 166 ms from the same actor depicted in the covert image, and the ISI was 1500 ms. Rest blocks that displayed a blank screen with a fixation cross and lasted 10 s were additionally included. The task was presented in two runs, each lasting ~8 min, during which each block type was presented 5 times. We conducted parallel analyses on the contrasts of covert fear vs covert neutral, overt fear vs overt neutral, and all fear vs all neutral blocks.

1.4. Data analysis

fMRI Data. For the threat processing task, the task design matrix consisted of columns for the four task blocks (overt fear, overt neutral, covert fear, covert neutral). We modeled a 19 s hemodynamic response function explicitly using cubic splines (AFNI's 3dDeconvolve with 'CSPLINzero' option for HRF fitting) with 10 parameters, separately for each block type, and accounting for serial correlation (AFNI's 3dREMLfit). Functional activation (height and width of HRF) during each block type was characterized with area-under-the-curve analyses using numerical integration (Lenow et al., 2014; Urry et al., 2006).

To assess task-modulated functional connectivity for fear vs neutral trials during the threat processing task, we used generalized psychophysiological interaction (gPPI) analyses (Cisler et al., 2014a; McLaren et al., 2012) using the amygdala clusters identified in the task activation analyses as seed regions (Supplemental Material).

Identifying pre-treatment fMRI predictors of symptom change. Second-level analysis consisted of whole-brain, voxel-wise, robust regression(Wager et al., 2005) analysis, in which the β coefficient representing slope of PTSD symptom change across time for each participant is regressed simultaneously onto 1) the voxel's contrast value, representing relative % signal change to fear vs neutral trials, and, 2) the intercept from the within-subject regression models representing severity of pre-treatment PTSD symptoms, in order to control for any confounding effects of pre-treatment symptom severity. To correct for multiple comparisons, we maintained a corrected $p < .05$ using cluster-level thresholding (Forman et al., 1995) defined with Monte Carlo simulation (AFNI's 3dClustSim), in which a significant cluster (corrected $p < .05$) is defined as a minimum of 51 contiguous voxels that survive a primary (uncorrected) threshold of $p < .01$.

We used two additional convergent measures of symptom change: slopes of changes in depression symptoms across treatment as measured by the SMFQ, and magnitude of pre-to post-treatment change in emotion regulation ability, as measured by the subscales of the DERS. Given that the DERS was only collected twice (pre and post-treatment), we could not calculate trajectory slopes comparable to the PTSD or depression symptom slopes.

We conducted parallel analyses for the measures of functional connectivity, in which the β coefficient representing slope of PTSD symptom change was regressed on the gPPI contrast values, again controlling for the intercept from the within-subject regression models representing severity of pre-treatment PTSD symptoms.

We focused analyses on those participants who received all modules of TF-CBT and had usable brain imaging data (n = 23). One participant's fMRI data was unusable due to motion artifact (see supplementary materials), and one participant was excluded due to incomplete brain coverage during fMRI scanning (i.e., excessive OFC and temporal lobe signal dropout). We additionally conducted

supplemental analyses among adolescents who completed ≥ four sessions (n = 28) (Supplemental Material).

2. Results

2.1. Treatment outcome

Mean pre- and post-treatment PTSD and depression symptoms, comorbid diagnoses, and DERS scores are reported in Table 1. Mean (*SD*) slopes of symptom change across treatment were −1.1 (.84) and −1.36 (2.42), among participants completing TF-CBT and participants receiving at least 4 sessions, respectively.

2.2. Treatment outcome and pre-treatment neural correlates of threat processing

2.2.1. Functional activation

Full results of analyses of functional neuroactivation are depicted in Fig. 1 and Table 2. We observed significant clusters of voxels in bilateral dorsal amygdala, extending dorsally into the striatum, where pre-treatment % signal change for all fear vs neutral blocks was significantly negatively related to slope of PTSD symptom change across treatment. For the contrast of covert fear vs neutral blocks, we similarly observed a significant cluster in the right amgydala where greater pre-treatment % signal change was significantly related to larger slope of PTSD symptom reduction during treatment. The contrast of overt fear vs neutral blocks failed to reveal any significant clusters. Fig. 2 displays the mean % signal change for fear and neutral blocks across all stimulus presentation formats among those participants with steep and shallow PTSD symptom slope β coefficients based on a median split.

We conducted additional analysis to further investigate the specificity of the relationship between % signal change in the amygdala ROIs and symptom reduction across presentation format (covert vs overt) and facial expression (fear vs neutral). These analyses (Supplemental Material) demonstrated similar effects when examining the contrast of covert fear vs covert neutral blocks and overt fear vs overt neutral blocks, and that there was no interaction between presentation format and facial expression.

Finally, given that the amygdala clusters extend dorsally into the striatum, we tested the effect specifically in the bilateral amygdala by using independently selected coordinates for bilateral amygdala taken from our previous study among adult women with PTSD (Cisler et al., 2014b) and again found significant bilateral clusters of activity related to PTSD symptom slopes (Supplemental Material and Supplemental Fig. 3).

2.2.2. Functional connectivity with amygdala during threat processing and treatment outcome

Given the observed relationships between amygdala activation to fear vs neutral faces and slope of treatment-related PTSD symptom trajectory, we extended the brain–behavior relationship by testing for patterns of whole brain functional connectivity with left and right amygdala during fear vs neutral face blocks that similarly scaled with PTSD symptom trajectory slopes using the gPPI method (Table 2). For both the right and left amygdala, we observed an overlapping significant cluster in the dorsal anterior cingulate cortex (dACC) where greater functional connectivity with the amygdala during all fear vs neutral blocks was associated with shallower slopes of PTSD symptom trajectories (Fig. 3). For the contrast of overt fear vs overt neutral blocks, we observe that heightened connectivity between right amygdala and right mid-posterior insular cortex was similarly associated with shallower slopes of PTSD symptom trajectories. For the left amygdala during this same contrast, we observed that greater connectivity with the visual cortex was associated with steeper slopes of symptom trajectory. For the contrast of covert fear vs covert neutral blocks, we did not observe any significant clusters.

To examine specificity of the dACC-amygdala connectivity with symptom reduction during fear and neutral blocks, we extracted the mean beta coefficients for the fear and neutral blocks separately for each participant in each significant dACC clusters and entered these as simultaneous predictors in the robust regression model (i.e., in place of the contrast variable). This analysis demonstrated, for both dACC clusters, opposing relationships of dACC-amygdala connectivity during fear and neutral blocks. During fear blocks, greater dACC-amygdala connectivity was related to shallower slopes of PTSD symptom trajectories (left amygdala-dACC: $\beta = .13$, $t = 4.5$, $p < .001$; right amygdala-dACC: $\beta = .25$, $t = 3.90$, $p = .001$). By contrast, during neutral blocks, greater dACC-amygdala connectivity was related to steeper slopes of PTSD trajectories (left amygdala-dACC: $\beta = -.1$, $t = -2.6$, $p = .016$; right amygdala-dACC: $\beta = -.22$, $t - 5.22$, $p < .001$).

2.3. Convergent validity for bilateral amygdala response as predictors of PTSD trajectories

We extracted mean % signal change values within these two amygdala/striatum clusters for each individual and tested with robust regression whether these values were also significantly related to additional measures of treatment outcome (Supplemental Figs. 3 and 4). For the right amygdala, pre-treatment % signal change for the general fear vs neutral contrast was

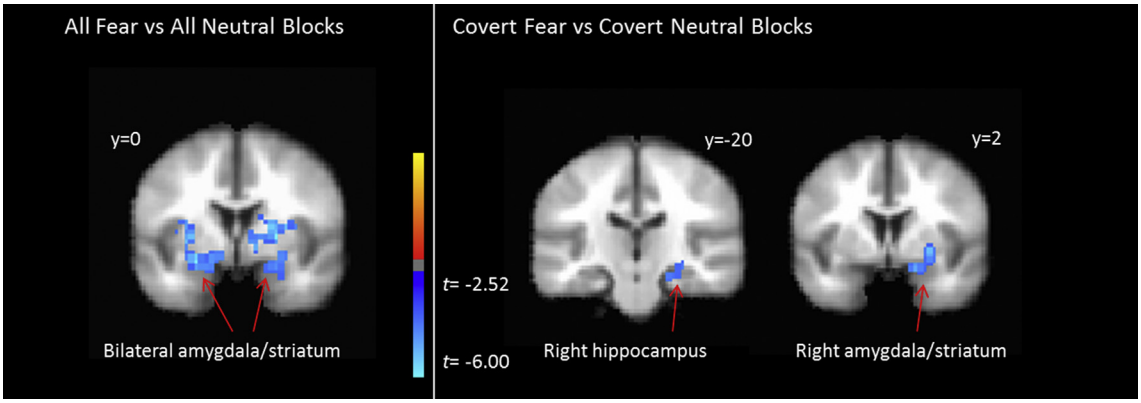

Fig. 1. Graphical depiction of significant clusters of voxels where activity for the contrasts of all fear vs neutral blocks (left) and covert fear vs neutral blocks (right) predicted slope of PTSD symptom trajectories. Negative relationships indicate that greater brain activity at pre-treatment is related to greater declines in PTSD symptoms across treatment.

Table 2
Significant clusters of voxels where pre-treatment % signal change for contrast of interest is related to PTSD trajectory slopes during TF-CBT.

Neuroimaging measure	Contrast	Anatomical label	X Y Z center-of-mass coordinates			Cluster size, voxels	Peak *t* value
			X	Y	Z		
Functional activation							
	All fear vs all neutral						
		Right amygdala/striatum	23	2	−3	193	−9.23
		Left amygdala/striatum	−22	−1	−7	137	−7.63
	Covert fear vs covert neutral						
		Right hippocampus	22	−32	−5	94	−4.34
		Right amygdala/striatum	26	3	−9	69	−5.26
	Overt fear vs overt neutral						
		No significant clusters					
Functional connectivity with right amygdala							
	All fear vs all neutral						
		Dorsal anterior cingulate cortex	12	16	32	51	4.77
	Covert fear vs covert neutral						
		No significant clusters					
	Overt fear vs overt neutral						
		Right mid-posterior insular cortex	50	−4	4	53	4.22
Functional connectivity with left amygdala							
	All fear vs all neutral						
		Dorsal anterior cingulate cortex	6	14	23	62	5.29
		Right posterior middle temporal gyrus	48	58	9	60	7.64
	Covert fear vs covert neutral						
		No significant clusters					
	Overt fear vs overt neutral						
		Occipital lobe	−17	−78	−13	89	−7.54

significantly related to the pre-to post-treatment decrease in the DERS subscales of 'difficulty engaging in goal-directed behavior during negative mood' ($\beta = 1.2$; $p = .002$), but not significantly related to symptom slopes for depression ($\beta = -.01$; $p = .99$). For the left amygdala, % signal change for the general fear vs neutral contrast was also significantly related to the pre-to post-treatment decrease in the DERS subscales of 'difficulty engaging in goal directed behavior during negative mood' ($\beta = 1.01$; $p = .02$), 'lacking strategies to regulate negative moods' ($\beta = 1.07$; $p = .02$), but not significantly related to symptom slopes for depression ($\beta = -.44$; $p = .67$).

2.4. Addressing effects of partial treatment completion and potential pre-treatment confounding factors

Pre-treatment bilateral amygdala activation to fear vs neutral faces were similarly significantly related to PTSD symptom trajectory slopes when including adolescents who received at least 4 TF-CBT sessions ($n = 28$; Supplementary Fig. 5).

When the primary analyses were repeated when including the possible pre-treatment confounding factors of age, verbal IQ, ethnicity, concurrent psychotropic medication (dichotomized into "yes" or "no"), total number of comorbid diagnoses, and assault severity (total number of assaultive event exposures), the observed relationships between pre-treatment left (all $ps < .0013$) and right amygdala (all $ps < .0079$) with subsequent PTSD symptom trajectory slopes remained significant. Similarly, the relationship between fear-modulated FC of the dACC with both the right (all $ps < .001$) and left (all $ps < .001$) amygdala remained significant when including these potentially confounding variables as covariates.

Aiding in interpretation of the amygdala functional activation findings, we observed opposing relationships between pre-treatment PTSD symptom severity and number of comorbid diagnoses with degree of bilateral amygdala activation: greater PTSD symptom severity was associated with greater fear vs neutral amygdala % signal change ($ps < .01$ for both left and right amygdala), whereas greater number of comorbid diagnoses (i.e., symptom complexity) was associated with less fear vs neutral amygdala % signal change ($ps < .013$ for both left and right amygdala).

3. Discussion

The present data suggest that individual differences within neurocircuitry mediating emotion processing predict symptom reduction during TF-CBT among assaulted adolescent girls with PTSD. Most notably given its role in salience detection, emotion, and centrality to neurocircuitry models of PTSD (Admon et al., 2013; Davis and Whalen, 2001; Rauch et al., 2006), we found that pre-treatment bilateral amygdala activation in response to fear vs neutral facial expressions was positively related to the course of subsequent PTSD symptom change; depressive symptom change was not predicted by reactivity in the amygdala ROI identified here. While the whole-brain analyses only revealed this relationship for the contrasts including all fear blocks and covert fear blocks, but not for overt fear blocks, the pattern of findings was similar across all stimulus presentation formats (Fig. 2) and there was no interaction between stimulus presentation and facial expression. The amygdala ROIs extended dorsally into the bilateral striatum, which is also widely implicated in salience processing (Zink et al., 2003, 2004, 2006), though follow-up ROI analyses did demonstrate the effect in the amygdala specifically. Demonstrating convergent validity, we also observed that pre-treatment bilateral amygdala activation was related to pre-to post-treatment improvements in specific domains of self-rated emotion regulation. Further supporting the robustness of the relationships between amygdala function and PTSD symptom change, this association could not be attributed to pre-treatment PTSD symptom severity, age, IQ, ethnicity, comorbidity, severity of assaultive event exposures, or concurrent medication, and similarly remained significant when including adolescents who received ≥4 sessions of TF-CBT. Nonetheless, it should also be explicitly mentioned that the lack of a no-treatment control group precludes inferences about predicting

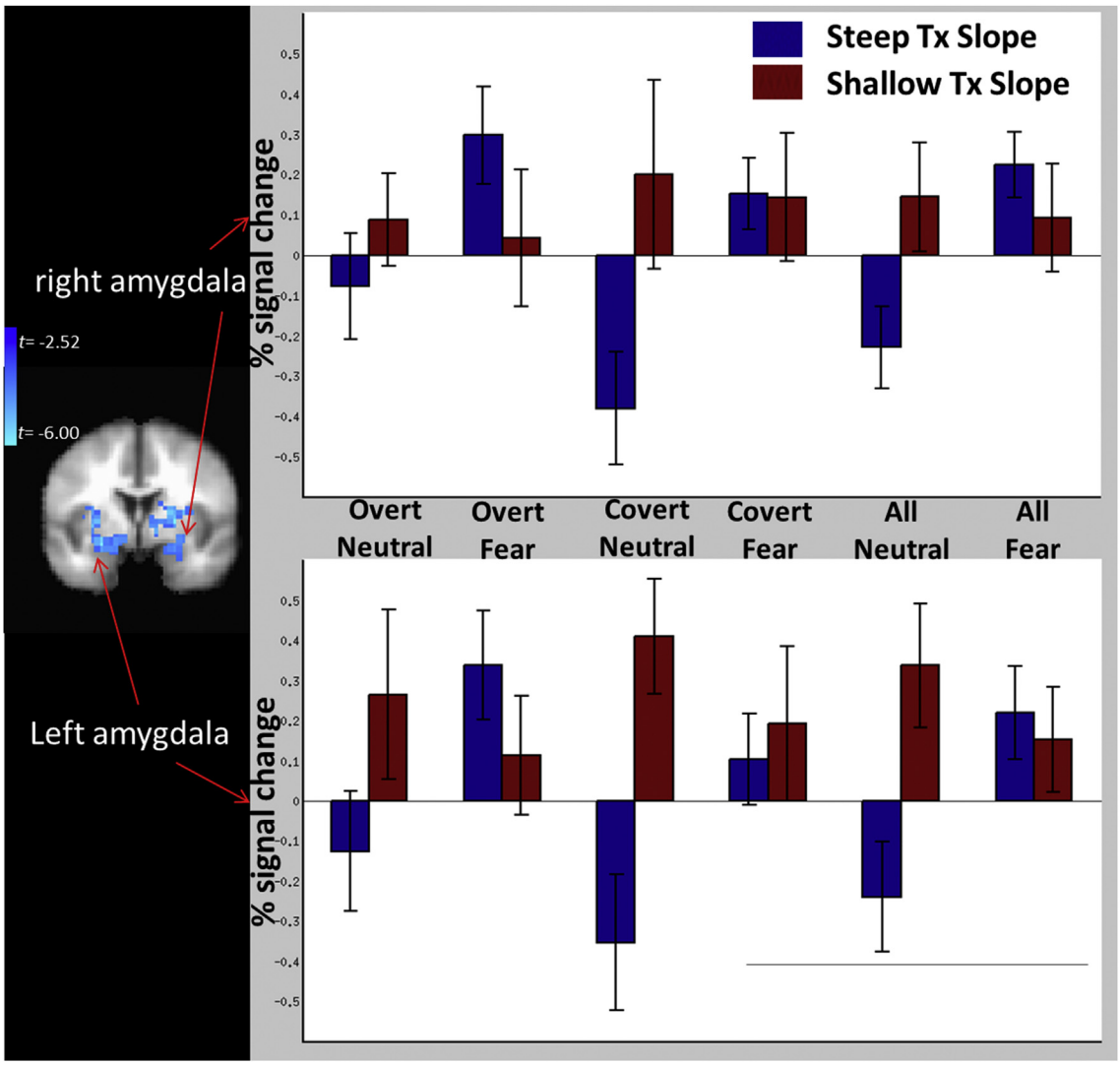

Fig. 2. Graphical depiction of activity for fear and neutral images separately as a function of shallow vs steep PTSD trajectory slopes across treatment and as a function of stimulus presentation formats for the right (top) and left (bottom) amygdala.

symptom change specifically versus predicting naturalistic/spontaneous symptoms reductions. These caveats should temper the following discussion accordingly.

Interestingly, adolescents who did better in treatment had greater pre-treatment amygdala reactivity to threat stimuli relative to neutral stimuli, whereas adolescents who did not respond as well in treatment demonstrated increased activity to both threat and neutral faces. These results have implications for neurocircuitry models of PTSD and for understanding interindividual variability in response to TF-CBT. Neurocircuitry models of PTSD invariably posit heightened amygdala responding to threat vs neutral (Admon et al., 2013; Rauch et al., 2006). Here, we observe that those adolescents who fit this model of neuropathophysiology by demonstrating hyper-reactive amygdala responses also had more severe PTSD symptoms and responded better to a psychological treatment that targets overt behavioral representations consistent with the implicated neurocircuitry. Concurrently, we also observed that assaulted adolescents with PTSD who exhibit increased amygdala activity to both threat and neutral stimuli, suggesting poorer amygdala discrimination between threat and safety, benefited significantly less from the same TF-CBT and tended to have greater symptom complexity (i.e., more comorbid diagnoses). These data highlight individual differences in neurocircuitry mediating PTSD (e.g., amygdala hyperactivity to threat compared to neutral vs non-specific amygdala hyperactivity) and demonstrate their impact on symptom reduction during TF-CBT.

A possible hypothesis regarding poorer symptom change among adolescents with increased amygdala activity to both neutral and threat stimuli is that threat-safety discrimination is a necessary prerequisite for symptom change during TF-CBT. It may be the case that in order for adolescents with PTSD to effectively learn and enact coping skills and to engage and process the traumatic memory, the adolescents first need to be able to discriminate safe signals. Indeed, emerging research among adults with PTSD demonstrates deficient safety signal learning and less contextual modulation of fear extinction memory consolidation (Garfinkel et al., 2014; Jovanovic et al., 2012). Nonetheless, we also observed that amygdala safety-threat discrimination is individually varying in this young PTSD sample, and that these individual differences predicted symptom reduction during TF-CBT. We also observed that at least two variables contributing to the individual differences in neurocircuitry is degree of symptom complexity (number of

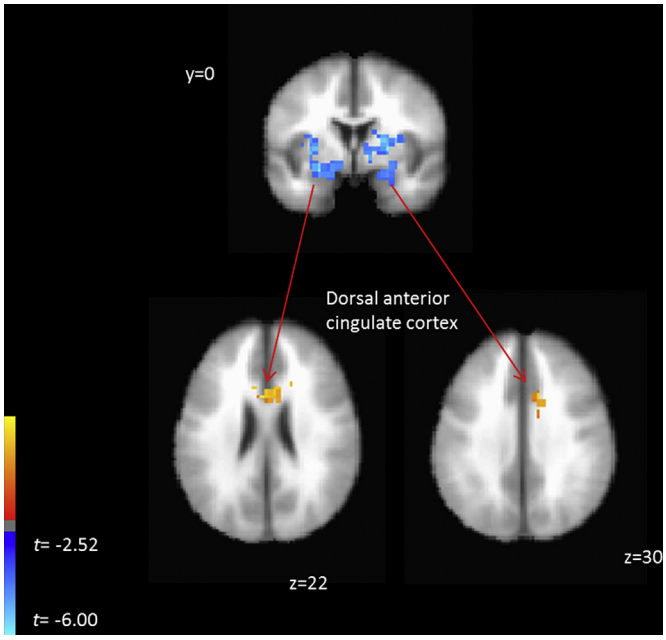

Fig. 3. Graphical depiction of significant clusters of voxels where functional connectivity with the left and right amygdala predicted slope of PTSD symptom trajectories. Positive relationships indicate that greater functional connectivity with the seed region was related to shallower slopes of PTSD symptom decline across treatment.

comorbid diagnoses) and PTSD symptom severity, which were related to lesser and greater differential processing of the amygdala for fear and neutral stimuli, respectively.

The results of the functional connectivity analysis demonstrate that greater fear-related connectivity between the bilateral amygdala and dorsal anterior cingulate cortex (dACC) was associated with worse symptom change, whereas greater connectivity during neutral blocks was associated with better symptom reduction. Functional interpretation of the dACC-amygdala functional connectivity relationships with symptom reduction is not straightforward. On the one hand, the dACC is reported to be hyper-reactive in PTSD (Admon et al., 2013; Patel et al., 2012) and generally implicated in threat appraisal (Etkin et al., 2011). On the other hand, the dACC also has been theorized to mediate the higher-order process of adaptive control (Shackman et al., 2011), which presumably subsumes more specialized functions to which the dACC is commonly linked (e.g., threat appraisal and conflict monitoring). Under this latter theory, the dACC's role is to integrate incoming information, such as from the amygdala, in order to bias information processing elsewhere in the brain and respond to task demands. In line with this theory, it might be plausible that the differential predictive relationships between dACC-amgydala connectivity and symptom reduction during fear vs neutral blocks is indicative of 'flexible' information processing, such that greater adaptability of the dACC-amygdala circuit to environmental demands (i.e., fear vs neutral stimuli) is a marker of adolescents who are more likely to succeed in cognitive-behavioral therapy that involves changing thinking and behavioral patterns.

To our knowledge, this is the first study examining the neurocircuitry of PTSD as predictors of symptom reduction during treatment for pediatric PTSD, though the study is not without limitation. The current study was limited in power and generalizability by a relatively small sample size, restriction to girls with assault-related PTSD, concurrent psychotropic medication among 43% of the sample, and lack of a no-treatment control group. Interestingly, a previous study among adults with PTSD found that heightened amygdala reactivity to threat relative to neutral stimuli was associated with *poorer* CBT treatment outcomes (Bryant et al., 2008a). While this prior study had a smaller sample size (N = 14), focused on a mixed-sex and mixed-trauma adult PTSD sample, and used a somewhat different treatment modality, the discrepant findings observed here among a homogeneous adolescent PTSD population and the previous study among adult PTSD highlights the need for replication and further research in this area. Future research along these lines is needed to elucidate more precisely the brain mechanisms of pediatric PTSD, their relationship with symptom change specifically, and to develop effective personalized treatments.

Contributions

Ben Sigel and Teresa Kramer were involved in study design, interpretation, and manuscript writing. Karin Vanderzee and Joy Pemberton were data collection, interpretation, and manuscript writing. Sonet Smitherman was involved in study design, data collection, and analysis. Clint Kilts was involved in study design, interpretation, and manuscript writing. Josh Cisler was involved in study design, analysis, interpretation, and manuscript writing.

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All authors report no financial conflicts of interest.

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Appendix A. Supplementary data

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