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

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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.

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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

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-