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Neural Substrates for Processing Task-Irrelevant Emotional Distracters in Maltreated Adolescents with Depressive Disorders: A Pilot Study

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Abstract

In this pilot study, neural systems related to cognitive and emotional processing were examined using event-related functional magnetic resonance imaging in five maltreated youth with depressive disorders and eleven non-maltreated healthy participants. Subjects underwent an emotional oddball task, where they detected infrequent ovals (targets) within a continual stream of phase-scrambled images (standards). Sad and neutral images were intermittently presented as task-irrelevant distracters. The maltreated youth revealed significantly decreased activation in the left middle frontal gyrus and right precentral gyrus to target stimuli and significantly increased activation to sad stimuli in bilateral amygdala, left subgenual cingulate, left inferior frontal gyrus, and right middle temporal cortex compared to non-maltreated participants. Additionally, the maltreated youth showed significantly decreased activation to both attentional targets and sad distracters in the left posterior middle frontal gyrus compared to non-maltreated participants. In this exploratory study of dorsal control and ventral emotional circuits, we found that maltreated youth with distress disorders demonstrated dysfunction of neural systems related to cognitive control and emotional processing.

Keywords

maltreatment; distress disorders; fMRI; executive function; amygdala

Introduction

Posttraumatic depressive disorders are seen in traumatized children who may not make the threshold posttraumatic stress disorder (PTSD) diagnostic criteria, but nevertheless have impairing subthreshold PTSD symptoms (Carrion, Weems, Ray, & Reiss, 2002).

In depressive disorders, dorsal control circuits show reduced activity while ventral emotional circuits show increased activity during cognitive and emotional challenges

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(Drevets, Price, & Furey, 2008). The dorsal control and ventral emotional circuits are dissociable as shown in fMRI studies using the emotional oddball task (Wang, Huettel, & De Bellis, 2008; Wang, McCarthy, Song, & LaBar, 2005). These investigations demonstrate that adolescents and adults activate dorsal control circuits to rarely presented events (an odd event) that requires attention; and emotional circuits (i.e., the amygdala and ventral prefrontal cortex) to sad images or distracters during the task.

In this exploratory pilot study, we examined dorsal control and ventral emotional circuits using the emotional oddball task in maltreated youth with depressive disorders. We hypothesized that maltreated youth would show decreased dorsal control activity to targets and increased ventral emotional activity in response to sad distracters as compared to non-maltreated healthy adolescents.

Method

Participants

Five maltreated adolescents (3 females; mean = 15.5 SD 2.3, range 11.6 –18.1 years) with depression and child protective services reports of physical abuse (without head trauma) and neglect and 11 non-maltreated adolescents (5 females; mean = 12.8 SD=3.3, range 10.7 –18.1 years) underwent the emotional oddball task during fMRI scanning. Groups did not differ in gender, socioeconomic status, IQ (mean maltreated = 110, SD=7.0 vs. non-maltreated mean = 118, SD= 20.5; p=.4), handedness, or age (p>.1).

Subjects and their legal guardians were interviewed using a modified version of the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997). For further diagnostic method details, see (M.D. De Bellis, Hooper, Spratt, Woolley, & Shenk, 2010).

Each maltreated youth had a current depressive disorder: major depression (n=3), dysthymia (n=1), and depressive disorder NOS (n=1). Mean age of onset of depressive disorders were 12.7, SD = 3.3 years. Current co-morbidity included PTSD (n=2), attention deficit hyperactivity disorder (n=1), and oppositional defiant disorder (n=1). Three maltreated youth had a past history of alcohol and cannabis use disorders. The mean last alcoholic drink = 273 days prior to scan, SD = 35.4 days (range 300–370 days) and mean last use of cannabis was 332 days prior to scan, SD = 157.8 days prior to scan (range 90–371 days). Mean age of onset of alcohol use disorder = 15, SD= 1.7 years and cannabis use disorder = 15.2 years, SD =1.9 years, which postdated their depressive disorders.

Exclusion criteria were: 1) medical illness; 2) schizophrenia or pervasive developmental disorder; 3) birth weight under 5 lbs or NICU stay; 4) current alcohol or substance use disorders; 5) use of psychotropic medications; and 6) full scale IQ < 85.

Controls were recruited from the community. Exclusion criteria were the same as above except controls had no history of maltreatment or DSM-IV Axis I disorders.

This study was approved by the University IRB. After a complete description of the study was given, written informed consent/assent were obtained from participants. Subjects received monetary compensation for participation.

Experimental Design

The experimental design, imaging and analytic procedures were identical to our study of healthy adolescents (ten of whom served as controls in this study) and healthy adults; see (Wang, et al., 2008) for further details. Briefly, the emotional oddball paradigm contained four stimuli: ovals (targets, 3.33%), sad photographs (emotional novels, 3.33%), neutral photographs (neutral novels, 3.33%), and phase-scrambled photographs (standards, 90%). Using scrambled pictures as a standard allows us to reduce inner mentality while participants await the next rarely presented stimuli. The sad photographs demonstrated crying or sad facial expressions. The neutral pictures had no emotional expressions, but were matched with the sad photographs on gaze direction, gender, posture, and number of individuals. The imaging session consisted of 10 runs, containing 150 stimuli. Stimulus duration was 1500 ms. Inter-stimulus interval was 500 ms. Interval between successive rare stimuli (targets and/or distracters) was randomized between 18 and 22 seconds to allow hemodynamic responses to return to baseline. Participants pressed a button upon detection of target stimuli. See Figure 1.

Image Acquisition

An oblique spoiled gradient-recalled acquisition sequence (three-dimensional, whole-brain), acquired parallel to the anterior commissure and posterior commissure plane, was used to collect high-resolution T1-weighted structural images (repetition time, TR: 12.3 ms; echo time, TE: 5.4 ms; field of view: 24 cm; flip angle: 20°; image dimensions: 256×256×68; voxel size: 0.975×0.975×1.9mm) on a 1.5 Tesla GE scanner. The functional images were acquired using an inward-spiral gradient echo pulse sequence (TR: 2000 ms, TE: 35 ms, FOV: 24 cm, flip angle: 90°, dimensions: 64×64×34, voxel size: 3.75 ×3.75×3.8 mm isotropic voxels).

Subjective ratings of sadness

Participants rated each picture on a scale corresponding to: `mildly happy', `neutral', `mildly sad', `sad', and `very sad' after MRI scan. Only images rated as `sad' or `very sad' by the participant were included in the data analysis for that participant These images were combined to constitute a `sad' category and were compared to images rated as `neutral' by the participant.

Voxelwise FMRI data analysis

Functional images were temporally adjusted for interleaved slice acquisition, corrected for head motion, co-registered to the high-resolution anatomical scan, normalized to a standard stereotaxic space, and spatially smoothed with a 8-mm isotropic Gaussian kernel (SPM; Wellcome Department of Cognitive Neurology, London, UK). Voxelwise analyses were conducted using custom software (Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC). The event epochs consisted of a total of 13 time points (−4s prior to 20s after stimulus onset with the average of −4 to 0s as baseline). A random-effects analysis was performed for the contrasts of sad vs. neutral and target vs. neutral at peak time point (6 s after stimulus onset). Two-sample t-tests were conducted to compare peak mean voxel-wise signal changes between groups at each stimulus condition (sad, neutral, and target), threshold at $p < 0.001$ uncorrected with a spatial extent of five contiguous voxels to avoid a false discovery (Genovese, Lazar, & Nichols, 2002).

Region-of-Interest (ROI) FMRI Data Analysis

Only independent clusters which showed a significant difference in the two-sample t-test analyses in dorsal control and ventral emotional regions were identified as regions of interest (ROIs). The stimulus type (sad, neutral, target) effect on percent signal change at the peak time point was analyzed using repeated-measures ANOVA and ANCOVA using age as covariate. Post-hoc tests were conducted using Bonferroni-corrected dependent *t*-tests. An alpha level of $p < 0.05$ was used for all ROI analyses.

Results

Behavioral analysis

The mean reaction time to attentional targets, image ratings, percentage of correct responses, and omission error rates did not differ between the groups indicating similar task performance.

Decreased Activation to Attentional Targets and Increased Activation to Sad Distracters in the Maltreated Depressed Group

Voxelwise two sample t- tests revealed significantly decreased activation to attentional targets (target vs. neutral) in maltreated youth relative to healthy participants in executive control circuits including the left middle frontal gyrus (MFG, BA9, peak Montreal Neurological Institute (MNI) coordinates, [x=−35,y=18,z=39], $t_{14} = 3.25$, $p < .001$) and right precentral gyrus (BA6, [−53,−4,25], $t_{14} = 4.66$, $p < .001$). In contrast, the maltreated youth had significantly increased activation to sad distracters (sad vs. neutral) in ventral emotional circuits including bilateral amygdala (Figure 2, left [−25,−11,−14], t =4.54, $p < .001$; right, [25,−4,−14], $t_{14} = 4.10$, $p < .001$) left subgenual cingulate (BA25, [−14,14,−21] $t_{14} = 6.27$, $p < .001$), left inferior frontal gyrus (IFG, BA47, [−46, 25, 4], $t_{14} = 3.47$, $p < .001$), and right middle temporal gyrus (MTG, BA21, [63,−7,−7], $t_{14} = 4.94$, $p < .001$) in comparison with non-maltreated youth. We also found maltreated youth had significantly decreased activation to both attentional targets and sad distracters in the left posterior MFG (pMFG) than controls indicating dysfunction in this ROI. See Figure 2. ANCOVA ROI analyses revealed that the above results were still significant after controlling for age.

We found the maltreated youth with depressive disorders had both significantly decreased activation to attentional targets in cognitive control circuits (left middle frontal gyrus and right precentral gyrus) and increased activation to sad distracters in ventral emotional circuits (bilateral amygdala, left subgenual cingulate, left inferior frontal gyrus, and right middle temporal gyrus) relative to controls during the emotional oddball task. Also, we found the maltreated youth had significantly decreased activation to both attentional targets and sad distracters in the left pMFG compared to controls indicating dysfunction of this region. In contrast to adults, healthy adolescents specifically activated bilateral pMFG by both attentional targets and sad distracters indicating an inhibitory role for pMFG during emotional distraction in adolescents (Wang, et al., 2008). Our findings in maltreated youth with depressive disorders indicate dysfunction in the process of inhibiting emotional distraction in the pMFG.

These findings were not due to differences in task performance between groups. This is the first neuroimaging study to report dysfunctional cognitive and emotional processing in maltreated youth with depressive disorders. The dorsal findings here are consistent with a study in adolescents with major depression (Halari et al., 2009). Our findings of increased amygdala and subgenual cingulate activity agree with previous findings of increased emotion processing in adolescent major depression (Beesdo et al., 2009; T. T. Yang et al., 2010). These studies of adolescent depression did not report maltreatment status. Our findings extend these findings to maltreated adolescents with depressive disorders, not all of whom made major depression criteria.

The study reported here must be considered preliminary because of the lack of a comparison group of maltreated children without depressive disorders. We do not know if our results are related to depressive disorders, co-morbidity, maltreatment, or their interaction. Although some maltreated participants had a history of alcohol and cannabis use disorders, these disorders were in remission prior to scanning. Co-morbidity in psychiatric disorders is commonly seen in maltreated children and is inherent to the field (M.D. De Bellis, 2001).

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This was an exploratory pilot study. Further research will advance a better understanding of cognitive control and emotional processes in maltreated youth.

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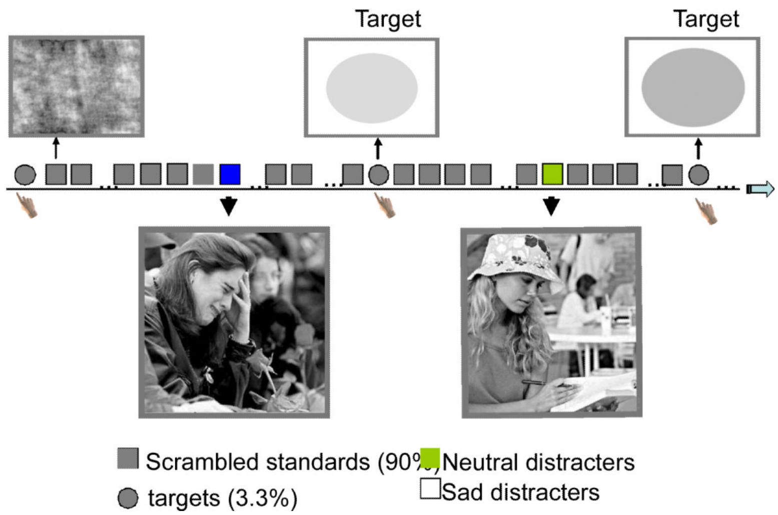

Figure 1.
The emotional oddball task. Participants pressed a response button upon detection of a rarely presented target stimulus, an oval, which requires attention and response selection. The target occurs rarely after more common scramble pictures or less common emotionally sad or neutral images appear as distracters.

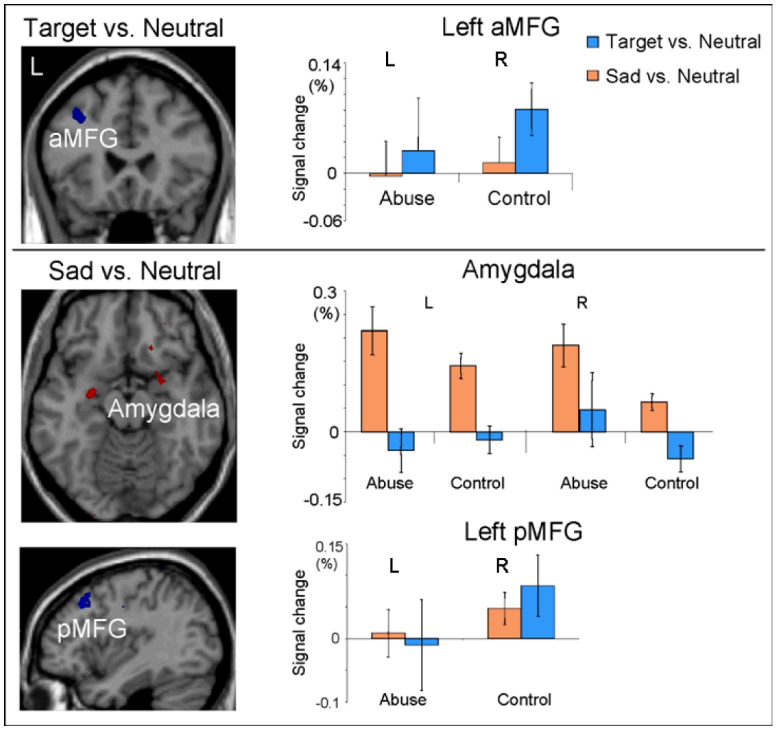

Figure 2. Group differences in response to the emotional oddball task

Left panel: The voxelwise two sample t test analyses in comparison of peak activation in response to attentional targets (target vs. neutral) and sad distracters (sad vs. neutral) between maltreated adolescents with depressive disorders and the control groups ($p < 0.001$ uncorrected, extent of five contiguous voxels). Maltreated adolescents with depressive disorders showed significantly decreased activation (blue) in the left anterior middle frontal gyrus (aMFG) to attentional targets, increased activation (red) in bilateral amygdala to sad distracters, and decreased activation (blue) in the left posterior middle frontal gyrus (pMFG) to both attentional targets and sad distracters.

Right panel: Peak signal percentage change in the maltreated adolescents with depressive disorders and control groups at each ROI as shown in the left panel. Light blue: the Target versus Neutral contrast; Orange: Sad versus Neutral contrast.