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Preliminary communication

Association between depression severity and amygdala reactivity during sad face viewing in depressed preschoolers: An fMRI study

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ABSTRACT

Background: Previous research has indicated that symptom severity and amygdala reactivity during the viewing of facial expressions of emotion are related in depression. However, it remains unclear how early in development this can be detected.
Methods: A sample of 11 depressed preschoolers (4.5 ± 0.8; 6 males) participated in an fMRI experiment where they viewed facial expressions of emotion. A region of interest approach was used in order to examine the relationship between amygdala activation and depression severity. Additional whole-brain analyses were conducted and the results of these analyses were examined for potential relationships with depression severity.
Results: Findings indicated that depressed preschoolers exhibited a significant positive relationship between depression severity and right amygdala activity when viewing facial expressions of negative affect. In addition, we found a significant positive relationship between degree of functional activation in the occipital cortex while viewing faces and level of depression severity.
Limitations: Additional research including a larger sample of depressed preschoolers, as well as a healthy comparison group, is needed to replicate the current findings and examine their specificity at this age.
Conclusions: This is the first study directly examining brain function in depressed preschoolers. The results suggest that, similar to older children and adults with depression, amygdala responsivity and degree of depression severity are related as early as age 3.

1. Introduction

The critical need for understanding functional and structural brain development abnormalities in *very early* onset mental illness is becoming increasingly clear (Davidson and Slagter, 2000; Pine et al., 2002). However, few studies to date have directly addressed this question due to greater diagnostic ambiguity in young children and the associated difficulty of translating developmentally appropriate tasks into an MRI environment. As such, the current study sought to begin filling this gap in the field by examining functional brain activation in the earliest empirically validated occurrence of depression, preschool onset major depressive disorder (PO-MDD).

Luby et al. (2002) have provided empirical evidence validating PO-MDD in a number of areas, including findings of symptom specificity discriminating PO-MDD from other early onset disorders, familial transmission (Luby et al., 2002), biological correlates (Luby et al., 2003), impairment across multiple contexts (Luby et al., 2009a), and longitudinal stability (Luby, 2009). Additionally, recent evidence has demonstrated continuity of PO-MDD with the well-known school age form of MDD, suggesting that depression identified during the

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preschool years is an earlier manifestation of MDD, rather than a transient or non-specific phenomenon (Luby et al., 2009b). This finding of homotypic continuity is of particular importance because it suggests that alterations in brain function that have already been documented in school age children (Zalsman et al., 2006) with depression may already be present earlier in development during the preschool period. The earliest possible detection of brain changes in depressive disorders is important to capture windows of opportunity for earlier interventions or prevention during periods of greater neuroplasticity.

Neurobiological models of depression have pointed to the importance of subcortical limbic structures, especially the amygdala, in the onset and course of the disorder. While our understanding of the amygdala is continually evolving, it is largely agreed that it plays a prominent role in the perception and expression of emotion (Phelps and LeDoux, 2005). Research into amygdala function in depression has been examined in a number of ways, including constrained (e.g., 'How sad?') or unconstrained (e.g., passive viewing) processing of human facial expressions of emotion (Peluso et al., 2009; Suslow et al., 2010). The frequent use of facial expressions in the study of MDD has been due in large part to their ecological validity as critical mediators of nonverbal communication across a large age range (Russell and Bullock, 1985; Birmaher et al., 2009; Ekman, 1993). Generally, studies incorporating these stimuli have indicated a heightened level of amygdala activity following exposure to facial expressions of negative emotion (e.g., sad) in MDD (Beesdo et al., 2009; Suslow et al., 2010). Additionally, individual differences in MDD severity and amygdala activity have been found to be positively related in both older children and adults during such tasks (Peluso et al., 2009; Belden et al., 2009).

Nevertheless, despite this growing body of literature on brain function in child, adolescent and adult MDD, data informing the neurodevelopmental course of brain function in general, and the function of the amygdala specifically, in PO-MDD has been unavailable to date. As an initial effort to begin addressing this need and stimulate further research, the current study reports on a group of young children with PO-MDD who underwent functional magnetic resonance imaging (fMRI) while viewing facial expressions of emotion. Following previous studies of emotion face processing in depressed adults using a region of interest approach (e.g., Sheline et al., 2001), we hypothesized that a positive relationship between MDD severity and amygdala activity would be found in children with PO-MDD when viewing facial expressions of sadness. Additionally, given the growing evidence supporting the involvement of cortical and subcortical areas in face processing, exploratory whole-brain analyses were conducted (Fusar-Poli et al., 2009). Based on previous research indicating a significant role for primary visual cortex during face viewing in similarly aged children (Gathers et al., 2004), it was hypothesized that functional activation within the occipital cortex would be found.

2. Methods

2.1. Participants

Participants included 14 preschool children with PO-MDD recruited as part of an ongoing federally funded treatment study (PI: J.L.). All children participated in the current imaging experiment prior to starting active treatment. Neurological disorders (e.g., seizure disorder, closed head injury, etc.), presence of an autism spectrum disorder, IQ<70, and ongoing participation in psychotherapy and/or taking psychotropic medication acted as exclusionary criteria (due to the treatment aims). Of the 14 children, data was not available for 3 due to excessive in-scanner movement during data acquisition. As a result, the final analyses included 11 children (average age: 4.5 ± 0.8 years; 6 males). Handedness was reported for 7 of these children (6 R).

2.2. Diagnostic assessment

Diagnostic assessments were conducted using the Preschool Age Psychiatric Assessment (PAPA) (Egger et al., 1999, 2003), an interviewer-based instrument with established test–retest reliability for use with caregivers of children between 2.0 to 6.0 years of age (Egger et al., 2006). The PAPA assesses for DSM-IV Axis I disorders in preschoolers using developmentally appropriate symptom manifestations. In addition, ratings of symptom severity, frequency, duration and resulting impairment are also collected during the interview. Following completion of the PAPA by trained research assistants, empirically derived DSM-IV algorithms applying relevant symptom and developmentally adjusted duration criteria (i.e., strict 2 week requirement not applied) gathered during the interview were used to generate MDD diagnoses. Any questions or discrepancies were reviewed and ultimately determined by a child psychiatrist (JL).

2.3. Depression severity scores

As a measure of depression severity, the number of MDD symptoms endorsed on the PAPA were summed and then divided by the total number possible to create a severity score for each child. Previous research has indicated that dimensional approaches incorporating such scores are sensitive indicators of depression severity at this age (Luby et al., 2004).

2.4. Facial-emotion viewing task

To ease in-scanner demands placed on the children participating in the study, a modified version of a common facial-emotion viewing task in MDD research was used (Lau et al., 2009). As in prior studies of depression and facial-emotion viewing, the current task presented a series of faces varying in affective content (see Fig. 1). However, rather than being asked to identify a feature of the presented stimulus (e.g., 'boy'), a simple button press was required when a face appeared. In addition to being more 'child friendly,' a less constrained response was chosen because of growing evidence that heightened amygdala responses associated with MDD may be more apparent during such tasks (Monk et al., 2008, Fales et al., 2008). In each run, children were shown pictures of faces taken from the NimStim Set of Facial Expressions (NimStim; http://www.macbrain.org/resources.htm). Of the possible 43 unique individuals in the Nimstim, 21 were used and counterbalanced for gender and ethnicity. Children were shown neutral, happy, and sad facial expressions as well as pictures of their mother in short blocks of the same face type. The current study only

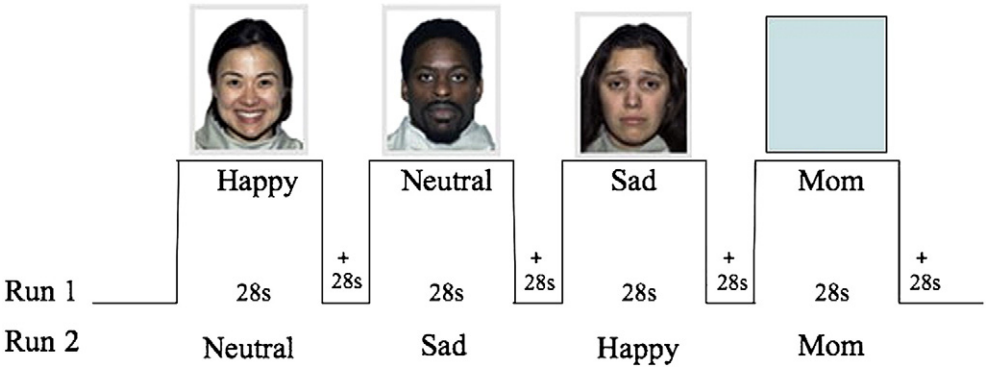

Fig. 1. Face viewing task and design. Four face viewing blocks (happy, neutral, sad, mom), each lasting 28 s, were presented in a counterbalanced fashion. Seven faces of the same face type were presented during each block. Within each block, the preschoolers were asked to push a button every time they saw a face. Blocks presenting a fixation cross were inserted between each face viewing condition. Each of the four viewing conditions was presented once per run, resulting in 28 trials per run. Each preschooler participated in two runs for an approximate total of 8 min functional scanning time.

reports on the sad, happy, and neutral face conditions. The mother condition will be the subject of a future report. Each face was shown for 3 s followed by a 1-second ITI. Each block contained 7 faces (28 s total) and the four blocks in each run (neutral, happy, sad, and mom) were interleaved with 28-second fixation blocks (see Fig. 1). Thus, each run was 3.8 min. Two runs were presented during each scan session for an approximate total of 8 min functional scanning time.

2.5. Functional imaging data acquisition and preprocessing

Imaging data were collected using a 3 T TIM TRIO Siemens whole body system. To create familiarity and comfort with study procedures, each child was provided with a child friendly video introducing the fMRI experience prior to their visit, allowed to scan a stuffed animal from the video, watch a movie of their choice during structural scans, and rewarded with small prizes following scan completion. Image acquisition included an initial low-resolution 3D sagittal T1-weighted MP-RAGE [TE = 1.13 ms, TR = 2.4 ms, flip angle = 8°, 1 acquisition, 128 slices, 3.3 × 2.5 × 2.5 mm voxels] rapidly warped to Talairach space (Talairach and Tournoux, 1988). This image was then used to provide on-line slice localization for the functional images, placing them as close as possible to the target template. T1 [sagittal acquisition, TE = 2.9 ms, TR = 6.6 ms, flip angle = 8°, 1 acquisition, 128 slices, 1 × 1 × 1 mm voxels] images were acquired as part of the structural imaging protocol and used in the transformation of images to a common template space (Talairach and Tournoux, 1988). The accuracy and validity of this transformation for children of this age was confirmed through visual inspection for distortions and the accuracy of alignment of key cortical and subcortical landmarks. The functional images were collected with a 12-channel head coil using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*) (TR = 2500 ms, TE = 27 ms, FOV = 256 mm, flip = 90°). During each functional run, sets of 32 contiguous axial images with isotropic voxels (4 mm^3) were acquired parallel to the anterior–posterior commissure plane. Stimuli were presented using PsyScope X on an Intel Macintosh computer, with each trial onset (face or cross hair) directly triggered by a pulse from the scanner. Images were projected onto a computer screen behind the child's head and viewed by a mirror positioned approximately 8 cm above the child's face. Participant responses were recorded via a fiber-optic button box interfaced with PsyScope X.

Prior to preprocessing, the first 4 frames of each run were discarded to allow for signal stabilization. The fMRI data were preprocessed using in-house Washington University software. Data were: 1) reconstructed into images and normalized across runs by scaling whole-brain signal intensity to a fixed value and removing the linear slope on a voxel-by-voxel basis to counteract effects of drift (Bandettini et al., 1993); 2) corrected for head motion using rigid-body rotation and translation correction algorithms (Friston et al., 1994; Snyder, 1996; Woods et al., 1992); 3) registered to Talairach space using a 12 parameter linear (affine) transformation; and 4) smoothed with a 6 mm FWHM Gaussian filter.

Estimates of functional activation during each condition were obtained using block-design analyses. This included the use of a general linear model (GLM) incorporating regressors for linear trend and baseline shift to estimate the hemodynamic response function for each stimulus type (i.e., facial expression). Within the GLM, a hemodynamic response shape was assumed (Boynton function) and used to derive magnitude estimates for each stimulus type relative to baseline fixation, which were then used in all subsequent statistical analyses.

2.6. Movement analysis

Within scan head movement was assessed using output from the rigid-body rotation and translation algorithm. After averaging the translations and rotations in the x, y, and z planes across frames, total root mean square (RMS) linear and angular measures were calculated for each run. Of the 11 participants, 4 demonstrated movement greater than 2 mm in any one direction during one or both runs. However, excluding these participants resulted in near identical results for the primary ROI analyses, with the exception being an additional relationship of significance during the neutral face viewing condition (see Results section). Thus, the analyses which are detailed later on included all 11 participants.

2.7. Functional imaging data analysis

2.7.1. Emotion viewing

To examine the relationship between depression severity and functional brain activity during facial-emotion viewing we used an ROI based approach, focusing on ROIs for the left and right amygdala derived from manually outlined anatomical templates. Previous studies using these ROIs have found abnormal activity in adults and children with depression (Fales et al., 2008; Rundle et al., in review; Belden et al., 2009). We averaged the signal across all voxels within each ROI to obtain a magnitude estimate for each one. As noted previously, separate depression severity scores for each child were calculated from the PAPA and used to examine the relationship between level of depression severity and functional activation in the amygdala. Given our a priori hypothesis stating a positive relationship between depression severity and amygdala activity and potential for a non-normal distribution, one-tailed Bonferroni corrected ($p = .008$) correlational analyses were conducted using Spearman's Rho (r) procedures.

2.7.2. Face viewing

We also conducted a whole-brain voxel-by-voxel analysis using data combined from the three face viewing conditions to explore activation related to face viewing (e.g., occipital gyri) and in other areas not captured by our a priori ROIs. Monte Carlo simulation was used in order to yield a combined p value/cluster thresholding corrected false positive rate of .05 uncorrected p value [<.0001] + cluster size thresholding [13 voxels]; (Forman et al., 1995; McAvoy et al., 2001). Significant area(s) of activation in the whole-brain analyses were converted to ROIs and used in post hoc analyses examining the correlation between depression severity score and magnitude of activation during face viewing. These correlational ROI analyses were orthogonal to the contrasts used to identify the ROIs, and thus are not subject to the "double-dipping" confounds described by Kriegeskorte and others (Kriegeskorte et al., 2009). A two-tailed approach to significance was used given the exploratory nature of these analyses.

3. Results

3.1. Behavioral

Due to inconsistent responding, behavioral data was unavailable for 1 participant. For the remaining participants ($N = 10$), the mean response time was 1337 ms (539) and the mean response rate was 98 (3.86) percent for the combined face viewing conditions (happy, sad, neutral).

3.2. Region of interest

The results from the ROI analyses indicated a strong positive relationship between MDD severity and level of activity in the right ($r = .709$, $p = .007$) but not left ($r = .421$, $p = .099$) amygdala during the viewing of sad faces (see Fig. 2). Activation in the right ($r = .416$, $p = .101$) and left ($r = .380$, $p = .125$) amygdala during the viewing of happy face faces did not correlate significantly with MDD severity. Similarly, activation in the right ($r = .302$, $p = .183$) and left ($r = .217$, $p = .261$) amygdala during neutral face viewing did not correlate significantly with MDD severity. However, it should be noted that the relationship between right amygdala activation and MDD severity during neutral face viewing did reach significance when analyses were conducted using the group defined by more conservative movement criteria ($r = .673$, $p = .049$; see Methods section). In addition, when participants with comorbid Separation Anxiety Disorder ($n = 4$) were removed, the relationships described previously remained, and significant relationships between right ($r = .685$, $p = .045$) and left ($r = .775$, $p = .02$) amygdala activity and MDD severity during happy face viewing were also present. No other comorbid internalizing disorders were present.

3.3. Whole brain

Similar to previous research (Gathers et al., 2004), whole-brain voxel level analyses revealed a large area of activity located primarily in the right inferior occipital gyrus (center of mass: x 17 y -92 z -3, BA 18, 290 voxels; see Fig. 2C) while viewing faces. No other areas of activation were found. A post hoc analysis examining the relationship between level of activity within this cluster during face viewing (i.e., sad + happy + neutral − baseline fixation) and MDD severity scores was significant ($r = .613$, $p = .045$). However, activation within this ROI did not reach significance for sad ($r = .494$, $p = .122$), happy ($r = .439$, $p = .176$), or neutral ($r = .508$, $p = .111$) face viewing conditions when examined separately, though the magnitudes of the correlations for each emotional condition were similar to each other and to the correlation with the average of the conditions.

4. Discussion

The current study sought to examine the relationship between *very early* childhood depression and functional brain activity in the amygdala and other regions responsive to face processing. To our knowledge, this is the first investigation of brain function in depressed preschoolers. As hypothesized, the current study found a positive relationship between level of MDD severity and amygdala activation in depressed preschoolers while viewing sad faces, a relationship that remained even after excluding children with comorbid SAD. This finding suggests that, similar to older children and adults with MDD, amygdala responsivity and degree of MDD severity are related even at this early age.

Notably, this relationship was significant only in the right amygdala. Previous studies examining amygdala activity and depression severity in older age groups have provided equivocal results regarding hemispheric lateralization (Abercrombie et al., 1998; Peluso et al., 2009). For example, mixed laterality effects have been reported in studies directly comparing MDD and healthy controls during both automatic and controlled face processing (Peluso et al., 2009; Lau et al., 2009; Suslow et al., 2010). However, for the current study, we believe that any conclusions about laterality should be undertaken with caution given the small sample size and the need for replication in a larger sample.

When considering facial expressions of emotion, the absence of a significant relationship between depression severity and amygdala activity in the complete sample while

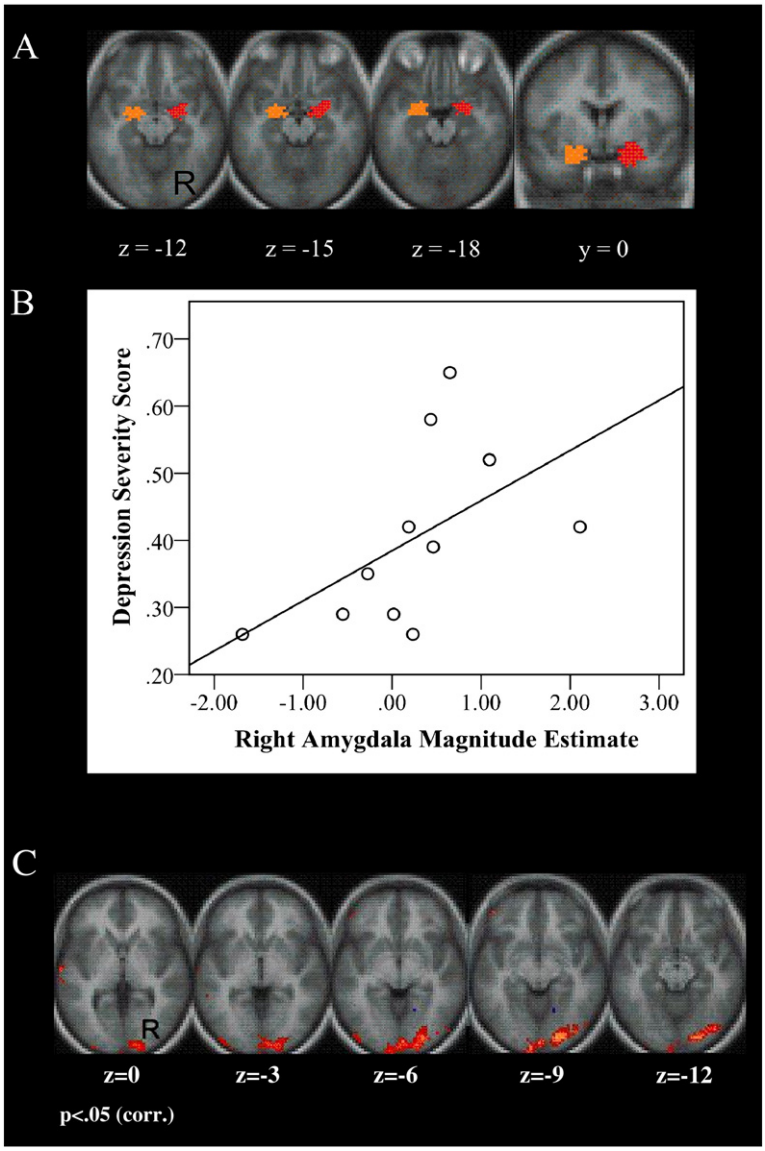

Fig. 2. Region of interest and whole-brain results. (A) Amygdala region of interest. (B) Correlation between right amygdala activity and depression severity. (C) Occipital activation identified during whole-brain analysis of face viewing and used in subsequent post hoc analyses. Note, R = right. Depression severity score represents proportion of symptoms endorsed.

viewing happy faces in the current study indicates this relationship may be stronger for expressions of negative emotions (e.g., sad). While speculative and in need of further exploration, this finding suggests that previously described negative biases in MDD may be present as early as the preschool period in affected individuals and observable at the level of functional brain activity. This conclusion is also potentially consistent with the finding of a positive relationship between amygdala activity during neutral face viewing and depression severity (when using a smaller subgroup with less movement). While a neutral facial expression is considered to be 'absent' of emotion, a number of studies have demonstrated that individuals with MDD perceive neutral faces as expressing greater levels of negative affect (Gollan et al., 2008; Gur et al., 1992). However, given our findings of a significant relationship between amygdala and happy face viewing when children with comorbid SAD were removed from the analyses, further research is needed to explore the specificity of enhanced amygdala activity in PO-MDD to negative stimuli.

Interestingly, our whole-brain analyses found a significant relationship between depression severity and greater functional activity within the right inferior occipital gyrus during face viewing. However, unlike the amygdala, the relationship between this inferior occipital activity and depression was very similar across the different emotion conditions and was less significant when examining each condition alone than when examining an average across all conditions. A recent meta-analysis has suggested that both the amygdala and inferior occipital gyrus, along with other areas, constitute part of a 'face processing' network (Fusar-Poli et al., 2009). Thus,

the current findings of a relationship between MDD severity and activity in both amygdala and inferior occipital regions during face perception suggests that early onset depression may influence multiple components of the systems that allow individuals to perceive, evaluate and respond to their interpersonal environment.

While the current study represents an important step forward in the study of early childhood depression, it will be important for future efforts to include larger samples of children with PO-MDD, as well as similarly aged healthy controls. Doing so would allow for the needed replication of the current findings, enable the exploration of their specificity to PO-MDD, and provide additional information concerning between diagnostic group differences in brain activity while viewing facial expressions of emotion. Additionally, future studies linking brain activity during ecologically valid task paradigms (e.g., face viewing) to other clinically relevant phenomenon (e.g., peer rejection) in PO-MDD will be pivotal in the development of models of the pathophysiology of this illness, as well as to prevention and treatment efforts. We are currently in the process of recruiting additional PO-MDD and healthy control participants in order to address some of the noted issues mentioned earlier.

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Conflict of interest

Dr. Barch has received grants from the NIMH, NIA, NARSAD, Novartis, and the McDonnell Center for Systems Neuroscience. Dr. Luby has received grants from NIMH and NARSAD. Dr. Belden has received funding from the McDonnell Center for Systems Neuroscience and NIMH (1K01MH090515-01). Dr. Gaffrey has received funding from the Klingenstein Third Generation Foundation. The remaining authors declare that they have no conflicts of interest to report.

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