Developmental Cognitive Neuroscience 17 (2016) 94–100

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Amygdala reactivity to sad faces in preschool children: An early neural marker of persistent negative affect

Michael S. Gaffrey[a,*], Deanna M. Barch[a,b,c], Joan L. Luby[a]

[a] Washington University in St. Louis, Department of Psychiatry, Campus Box: 8511, 660 South Euclid Avenue, Saint Louis, MO 63110, United States
[b] Washington University in St. Louis, Department of Psychology, Campus Box: 8511, 660 South Euclid Avenue, Saint Louis, MO 63110, United States
[c] Washington University in St. Louis, Department of Radiology, Campus Box: 8511, 660 South Euclid Avenue, Saint Louis, MO 63110, United States

ARTICLE INFO

Article history:
Received 27 May 2015
Received in revised form
28 December 2015
Accepted 29 December 2015
Available online 2 January 2016

Keywords:
Amygdala
Negative affect
fMRI
Irritability
Child
Development

ABSTRACT

Background: Elevated negative affect is a highly salient risk factor for later internalizing disorders. Very little is known about the early neurobiological correlates of negative affect and whether they associate with developmental changes in negative emotion. Such information may prove critical for identifying children deviating from normative developmental trajectories of negative affect and at increased risk for later internalizing disorders. The current study examined the relationship between amygdala activity and negative affect measured concurrently and approximately 12 months later in preschool-age children.
Method: Amygdala activity was assessed using functional magnetic resonance imaging in 31 medication-naive preschool age children. Negative affect was measured using parent report both at the time of scan and 12 months later.
Results: Negative affect at baseline was positively correlated with right amygdala activity to sad faces, right amygdala activity to happy faces, and left amygdala activity to happy faces. Right amygdala activity to sad faces also positively predicted parent-reported negative affect 12 months later even when negative affect reported at baseline was controlled.
Conclusions: The current findings provide preliminary evidence for amygdala activity as a potential biomarker of persistent negative affect during early childhood and suggest future work examining the origins and long-term implications of this relationship is necessary.

1. Introduction

Disrupted processing of negative affect is one of the most clinically salient characteristics of risk for later internalizing disorders, including depression and anxiety (Wilson et al., 2014; Karevold et al., 2009). Research continues to suggest that understanding early brain behavior relationships may be critical for the identification and prevention of later occurring psychopathology. However, very little is known about the neurobiological correlates of negative affect processing in very young children and whether such correlates can inform individual differences in negative affective reactivity at later time points. A large body of research consistently suggests that the amygdala plays an important role in the processing of emotionally salient information (Pessoa, 2010), and associations between heightened amygdala reactivity and elevated negative affect have been established in multiple study samples (Barch et al., 2012; Peluso et al., 2009; Henderson et al., 2014; Swartz et al., 2015). Nevertheless, very little is known about this relationship in early childhood and whether amygdala reactivity at this age is predictive of future negative affective behavior. Given the challenges associated with reliably measuring behavioral markers of negative affect at this age using common approaches (e.g., potential for biased parent report, failure to successfully elicit negative responses to lab-based challenges, etc.), the exploration of neural markers of negative affect may hold promise for identifying highly objective and potentially more robust early markers of risk. In addition, understanding the developmental neurobiology of negative affect is likely to clarify our understanding of elevated negative affect as a feature common to many psychiatric conditions and to further inform mechanisms of change in transdiagnostic treatments targeting early development (Insel, 2014).

Research examining the relationship between early negative affect and later internalizing psychopathology, such as anxiety and depression, has suggested that elevated negative affect during early childhood is an important marker of risk. For example, at the symptom level, infants rated as 'fussy' and 'difficult to soothe' by their parents are also more likely to have higher scores on maternal ratings of depression and anxiety at 5 years of age (Cote et al., 2009).

* Corresponding author.
E-mail address: gaffreym@wustl.edu (M.S. Gaffrey).

http://dx.doi.org/10.1016/j.dcn.2015.12.015

Similarly, high negative emotionality scores during the infancy and preschool periods have been associated with elevated parental ratings of anxiety and depression symptoms during later school age and adolescence (Karevold et al., 2009; Dougherty et al., 2011). More recent data suggest a similar phenomenon when diagnostic outcomes are considered. Specifically, elevations in negative affect at 6 years of age have been found to significantly increase the odds of receiving a diagnosis of depression at 18 years old (Bould et al., 2014). Studies investigating early irritability (i.e., easy annoyance and touchiness characterized by anger and temper outbursts) have also suggested a strong link between elevations in negative affect and later psychopathology. Of particular relevance for identifying young children at increased risk for psychopathology, a recent study reported that irritability measured at 3 years of age was predictive of depression and oppositional defiant disorder (ODD) diagnoses 3 years later (i.e., 6 years of age) over and above baseline diagnostic status (Dougherty et al., 2013). Further, using measures controlling for item overlap, the authors also found that irritability measured when children were 3 years old predicted increases in dimensional measures of depression, ODD, and functional impairment at 6 years of age.

Amygdala reactivity to emotional stimuli in healthy young children has been demonstrated (Gee et al., 2013; Todd et al., 2011; Perlman and Pelphrey, 2011), but to date only one has examined its relationship with early childhood psychopathology. A study of face processing in preschool age children with and without a very early occurring form of depression found increased activity in the right amygdala of depressed preschoolers (Gaffrey et al., 2013). Individual differences in negative affect and amygdala activity at this age were also explored. Heightened right amygdala activity while viewing facial expressions of emotion was found to be correlated with elevated parental reports of negative affect in both depressed and healthy preschoolers, matching the few dimensional studies of amygdala activity and depression severity in children and adolescents (Henderson et al., 2014; Barch et al., 2012). As such, this study suggested an important link between concurrent negative affect and amygdala function in preschool age children. However, it left unanswered whether amygdala activity during the preschool period is predictive of *future* negative affect, a key question for understanding whether trajectories of early emotional development and amygdala function are related.

The goal of the current study was to examine the relationship between amygdala activity during face viewing and negative affect at the time of scan (i.e., baseline) and approximately 12 months later in preschool age children. Based on our previous neuroimaging work including healthy and depressed preschoolers (Gaffrey et al., 2013), we expected that elevated amygdala activity while viewing facial expressions of emotion would be associated with increased parent reported negative affect at baseline. Further, given longitudinal studies suggesting the relative stability of negative affect across development (Neppl et al., 2010), we anticipated that such amygdala activity would predict unique variance in negative affect at follow-up. Given that fMRI research examining the relationship between negative affect and specific facial expressions of emotion in children has been limited, a strong a priori hypothesis as to which face type(s) would be related to parent reported negative affect was not made.

2. Methods

2.1. Study participants

Four-to-six year old children were recruited from pediatrician's offices, daycare facilities, and other community resources throughout the greater St. Louis metropolitan area using a screening checklist (Preschool Feelings Checklist (Luby et al., 2004) [PFC]) to identify preschoolers with elevated depressive symptoms and a healthy control group. Caregivers indicating that their preschoolers were at "low" ($\leq$1 PFC item endorsed) or "high" ($\geq$3 PFC items endorsed) risk for depression-related difficulties were contacted. Once contacted, an additional phone screening assessing for the presence of neurological disorders (e.g., seizure disorder, closed head injury), autism spectrum disorders, developmental delays, premature birth (<36 weeks gestation), and psychotropic medication use was completed. Endorsement of any of these conditions was exclusionary for all children. Using these screening criteria, 67 preschoolers were recruited into the study and 47 provided usable fMRI data. Of the 20 remaining children, fMRI data were lost because of failed QC (n = 18), equipment failure (n = 1), and discontinuation of scan per child request (n = 1). Baseline data from these 47 children has been previously reported on in (Gaffrey et al., 2013). Of the 47 children with usable baseline fMRI data, 31 agreed to participate in an additional follow-up assessment approximately 1 year later, including 5 meeting for preschool depression and 26 healthy control children. On average, follow-up assessments took place 364 ($\pm$87) days following the baseline appointment. Of the 16 children not included, 8 preschoolers with depression were subsequently enrolled into a treatment study following their baseline scan which prevented their participation and 8 (5 healthy controls and 3 preschool depression) were unable to be contacted or refused to participate. Preschoolers with PO-MDD who did not participate in a follow-up assessment were not different from those who did in parent-reported negative affect ($t[21] = -.493$, $p = .627$, 2-tailed) or amygdala reactivity to sad faces ($t[21] = -1.5$, $p = 0.15$, 2-tailed) at baseline. Parental written consent and child verbal assent were obtained for all subjects. The Institutional Review Board at Washington University in St. Louis approved all experimental procedures.

2.2. Diagnostic assessment

Diagnostic assessments were conducted at baseline using the preschool age psychiatric assessment (PAPA), a developmentally appropriate, interviewer-based instrument designed for use with the primary caregivers of children between 2 and 7 years of age (Egger et al., 1999, 2003). The PAPA includes all relevant DSM-IV (APA, 2000) criteria and their age appropriate manifestations, has established test–retest reliability (Egger et al., 2006), and is widely used to assess for DSM-IV Axis I disorders in preschoolers. Detailed training and calibration methods have been previously described (Luby et al., 2009). After completion of the PAPA by trained research assistants, relevant symptom, impairment, and duration criteria gathered during the interview were used to generate diagnoses, including preschool depression (PO-MDD; Luby et al., 2014). Children placed into the control group did not meet criteria for any DSM-IV Axis I disorder according to parent report on the PAPA.

2.3. Measure of child's negative affect

Parents completed the emotion regulation checklist (ERC; Shields and Cicchetti, 1997) at baseline and follow-up. The ERC is a parent report measure of children's dysregulated negative affect (Negativity) and successful emotion regulation, and includes both positively and negatively weighted items to be rated on a 4-point Likert scale. Given our specific hypotheses about amygdala function and negative affect, the Negativity (Cronbach's $\alpha = 0.84$) subscale was of particular interest and therefore was used in the analyses described below. The Negativity subscale is composed of 15 questions and possible scores range from 15 to 60 points. High scores reflect rapid changes in child mood (i.e., quickly moving from positive to negative moods), angry reactivity, and increased intensity of